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Functionalisable Cyclopolymers by Ring-Closing Metathesis

THE UNIVERSITY *of* EDINBURGH

University *of* Glasgow

Mohammed Alkattan
BSc, MSc Drug Chemistry

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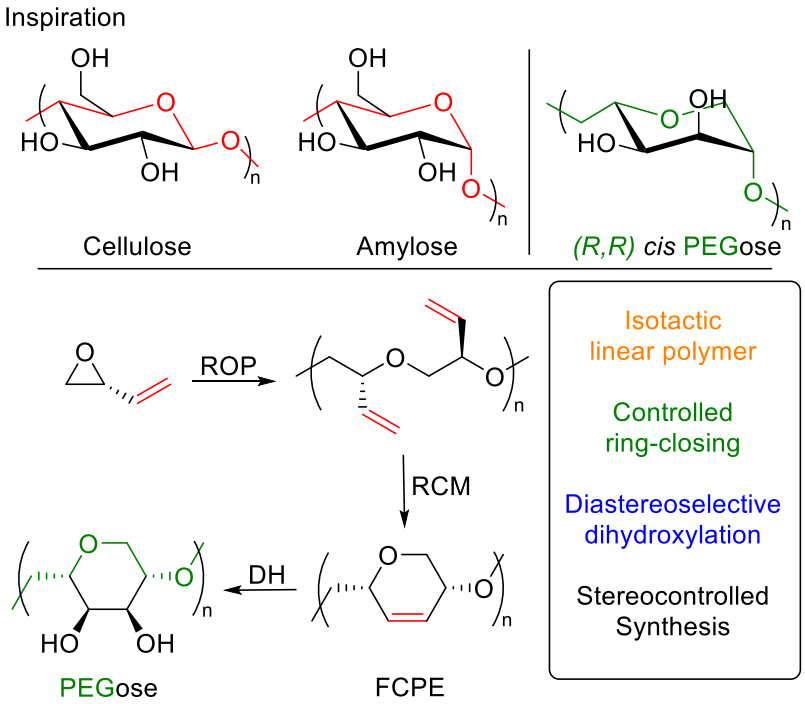
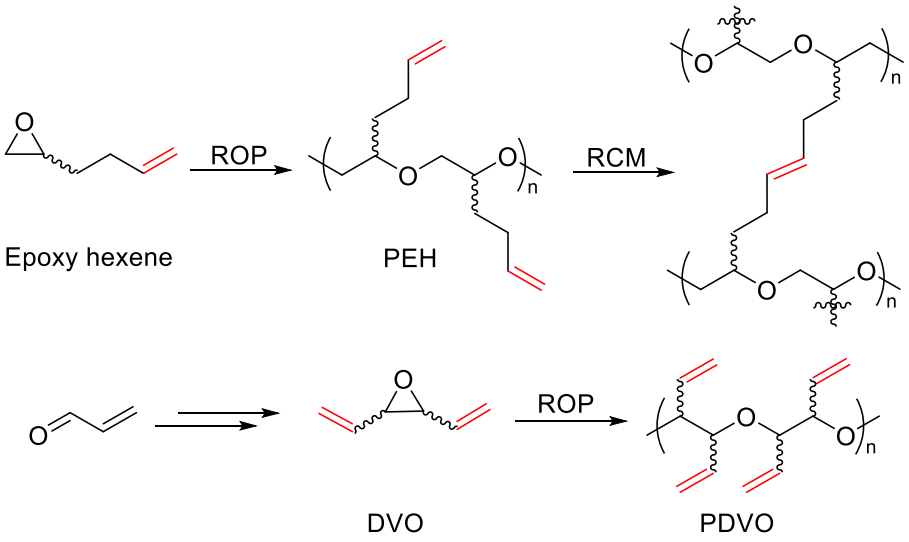
Abstract

Post-polymerisation modification of polymers is extremely beneficial in terms of designing brand new synthetic pathways toward functional complex polymers. While many chemical groups could provide a platform for chemical functionalisation, arguably one of the most versatile groups is the olefin functionality. This could be significant as the olefins do not readily interfere with common polymerisation techniques such as ring-opening polymerisation (ROP) but can be transformed into a broad range of functional groups. Ring-Closing Metathesis (RCM) is a powerful method for the preparation of cyclic compounds by the formation of new carbon-carbon double bonds. The aim of this project is utilising RCM as a post-polymerisation modification tool for preparing novel functionalisable cyclopolymers. This work includes monomer synthesis, ring-opening polymerisation and post-polymerisation modification. Whereas aliphatic polyethers are highly established polymers and used for an immense variety of applications, stereoregular cyclic architectures of polyethers mimic natural polymers remain rare in synthetic polymer chemistry. Herein we disclosed the formation of a stereocontrolled 1,4-linked six-membered functionalisable cyclopolyether (FCPE) prepared by RCM.

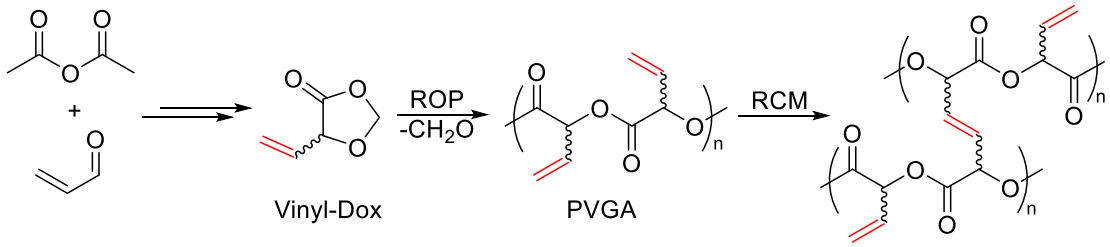


Further post-polymerisation modification by diastereoselective dihydroxylation (DH) afforded a novel polymer family encompassing a poly(ethylene glycol) backbone and sugar-like functionalities "PEGose". The high stereoregularity of FCPE and PEGose produced helical conformation structures. In particular, (*R*,*R*) *cis* PEGose structure has an extended pseudohelical structure similar to amylose.

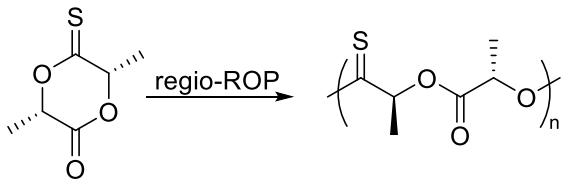
Different ring sizes of cyclopolyethers were sought from two other different starting polymers; poly(epoxy-hexene) (PEH) and poly(divinyl-oxirane) (PDVO). While divinyl oxirane (DVO) and epoxy hexene (EH) were successfully polymerised by ROP, the RCM of PEH gave mainly a cross-linked polymer.



The project also attempted to expand the principle to polyesters to afford 1,4-linked six-membered functionalisable cyclopolyesters. To have the desired structure, a novel polymer of poly(vinyl glycolic acid) (PVGA) was made by ROP of a new monomer, 5-vinyl-1,3-dioxolan-4-ones (vinyl-Dox), using an aluminium salen catalyst system. However, the RCM of the last polymer was not completed even after two days of the reaction and gave mainly a cross-linked polymer.



Finally, in a collaborative project, ROP of L-thionolactide was reported for the first time using aluminium salen catalysts. The polymerisation was controlled, regioselective and completed within a few hours.



Lay Summary

Natural polymers such as polysaccharide and polynucleotides literally dominate all spheres of life. Their unique architectures are the key elements crucial to their biological functions. Mimicking this type of polymers in synthetic polymer chemistry is still rare and challenging. Given this fact, much effort has been devoted to the development of efficient synthetic methods for production of polymers with well-defined architectures and topologies along with their structure-dependent properties.

The combination of organic synthesis with well-established polymerisation techniques opens pathways for the preparation of a library of polymers with well-defined architecture and tailor-made stereocontrolled functionalities. Ring-closing metathesis (RCM), a well-established reaction in organic chemistry, has been used a few times in post-polymerisation modification. This thesis used RCM to synthesise stereocontrolled and functionalisable cyclopolymers to mimic advanced materials for biomedical applications.

Stereocontrolled functionalisable cyclopolyethers were successfully prepared by RCM. The stereocontrolled cyclopolyethers produced showed a helical conformation. This polymer was further functionalised by dihydroxylation to afford a novel polymer, PEGose, mimicking structurally and conformationally the natural glucan, amylose.

Attempts were made to expand this strategy to polyesters. A novel monomer was synthesised and polymerised to afford poly(vinyl glycolic acid). However, the RCM of the produced polymer led to a cross-linked structure.

Finally, in a collaborative project, a novel polymer of L-thionolactide was made by a regioselective ring-opening polymerisation using aluminium salen catalysts.

Declaration

The work described in this thesis is of my own unless I have acknowledged help from a named person or referenced a published source. This thesis has not been submitted, in whole or in part, for any other degree.

Signature: 

Date: 04/02/2020

Acknowledgements

I would like to thank my supervisors Prof Michael P. Shaver and Dr Joëlle Prunet for giving me the chance to carry out my PhD in their prestigious research groups. I have been extremely lucky to work with both on this unique project. Over the last 4 years, they have always made time to guide and support me, so I am grateful for their supervision and encouragement.

My PhD has been made memorable by many members of the Green Materials Laboratory at the University of Edinburgh and I would like to say thank you to Dr Fern Sinclair, Dr Stefan Cairns, Dr Yuechao Xu, Dr Mitch Perry, Dr Emily MacDonald, Dr Meng Wang, Dr Ben Lake, Dr Jaclyn Raeburn, Dan Coward, Vishal Makwana, Geraint Langford and many others. Also, I would like to thank my lab mates in Raphael Lab at the University of Glasgow especially Alex Tiniakos and Carolina Ojeda-Porras.

Thanks also to all team members at the two schools of chemistry in Edinburgh and Glasgow Universities with a special acknowledgement to who helped with analytical support; Dr Lorna Eades, Dr Sharon Kelly and Dr Claire Wilson.

Lastly, a huge thank to my family and friends who have always believed in me and provided kind and supportive words during stressful times. In particular, I would like to thank my life-partner Aliaa. Her patience and understanding were unparalleled, and she made the hard days easier. We shared every moment and she always kept me smiling the whole way, I could not have done this without her.

Table of Contents

List of Abbreviations

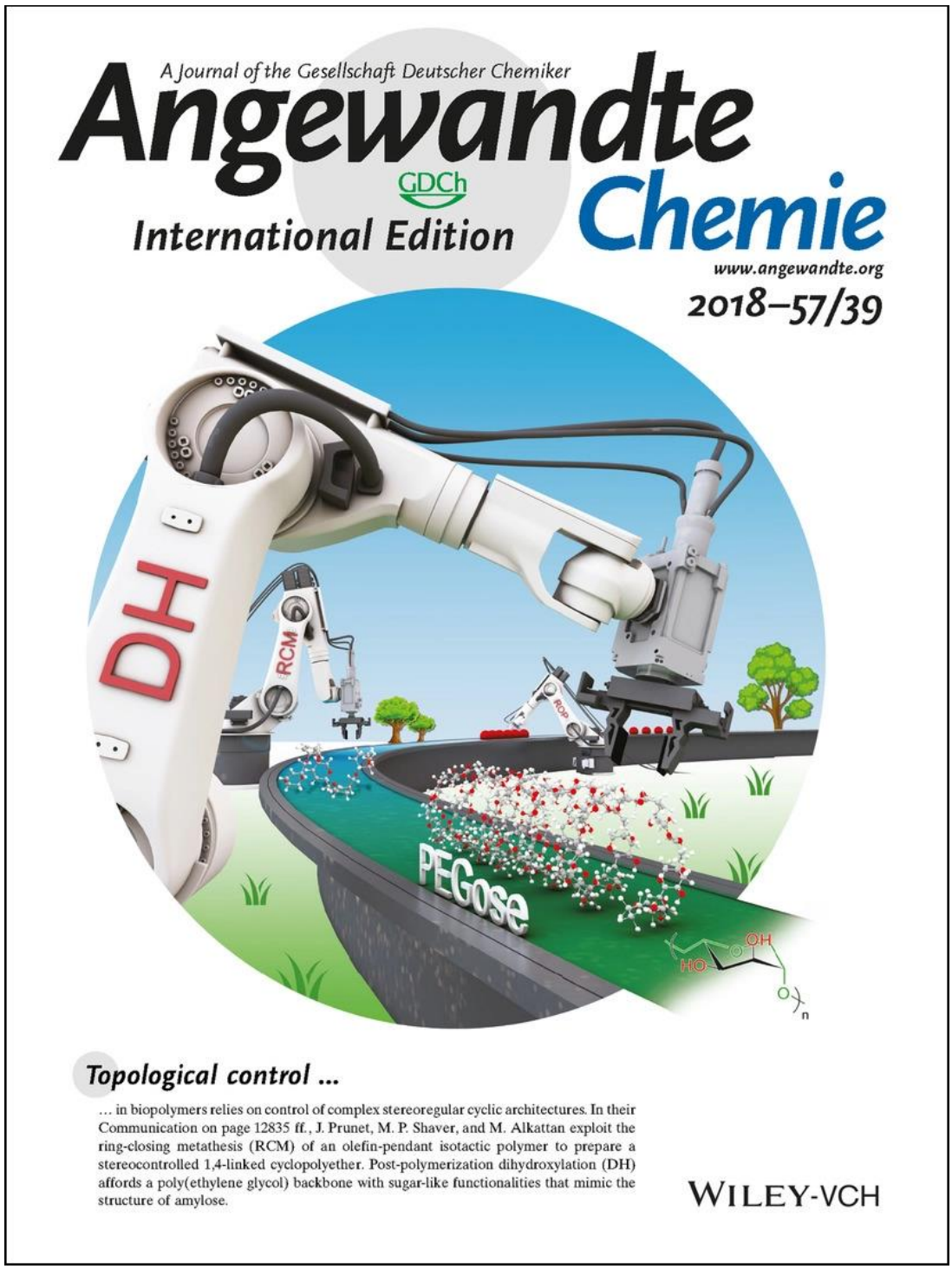
ADMET	acylic diene metathesis
Ar	Aromatic
Bn	benzyl
CM	cross-metathesis
*t*Bu	tertiary butyl
COSY	homonuclear correlation spectroscopy
Đ	dispersity
Cat.	catalyst
I	inititor
M	monomer
DBU	diazabicyclo[5. 4.0]unde-7-ene
DCM	dichloromethane
DCE	1,2-dichoroethane
DSC	differential scanning calorimetry
EO	ethylene oxide
EtOAc	ethyl acetate
ESI	electrospray ionisation mass spectrometry
FG	functional group
PVA	polyvinyl alcohol
PCL	poly(ε-caprolactone)
PEG	poly(ethylene glycol)
3D	three-dimensional
OM	olefin metathesis
ROM	ring-opening metathesis
OCM	olefin cross metathesis
ROMP	ring-opening metathesis polymerisation
CDP	cyclodepolymerisation
DMSO	dimethyl sulfoxide
PEO	poly(ethylene oxide)
PPO	poly(propylene oxide)

PPG	poly(propylene glycol)
EB	3,4-Epoxy-1-butene
mm	isotactic triad
DEE	diethyl ether
Me	methyl
DMF	dimethyl formamide
m-CPBA	*meta*-chloroperoxybenzoic acid
er	enantiomeric ratio
NHCs	N-heterocyclic carbenes
PEB	poly(epoxybutene)
FCPE	functionalisable cycolpolyethers
DH	dihydroxylation
(TPP)AlCl	tetraphenylporphyrin aluminium chloride
MAlBP	methylaluminum *bis*(2,4,6-tri-*tert*-butylphenolate)
Con.	conversion
GPC	gel permeation chromatography
HSQC	heteronuclear single quantum correlation
J	NMR coupling constant
LA	lactide
M_n	number average molecular weight
M_w	weight average molecular weight
MALDI	matrix assisted laser desorption ionisation
NMR	nuclear magenetic resonsance
Ph	phenyl
PLA	poly(lactic acid)
PLGA	poly(lactic-*co*-glycolic acid)
*i*Pr	isopropyl
rac	racemic
RCM	ring-closing metathesis
ROMP	ring-opening metathesis polymerisation
rt	room temperature
SEC	Size exclusion chromatography
T_c	crystallisation temperature

T_g	glass transition temperature
T_m	melting temperature
TBD	1, 5, 7-triazabicyclo[4. 4.0]dec-5-ene
THF	tetrahydrofuran

Publications

1- **M. Alkattan**, J. Prunet and M. P. Shaver, Functionalizable Stereocontrolled Cyclopolyethers via Ring-Closing Metathesis as Natural Polymer Conformation Mimics, *Angew. Chem. Int. Ed.* **2018**, *57*, 12835-12839.

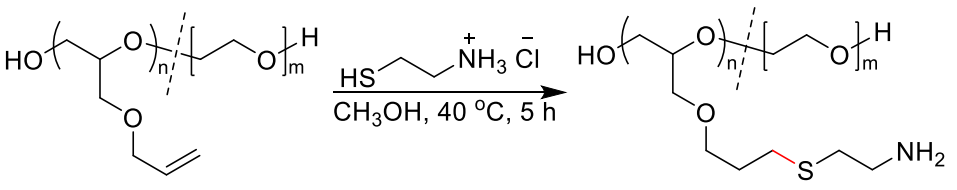


2- F. Sinclair, **M. Alkattan**, J. Prunet and M. P. Shaver, Olefin cross metathesis and ring-closing metathesis in polymer chemistry, *Polymer Chemistry* **2017**, *8*, 3385-3398.

Chapter 1. Introduction

1.1 Polymers and post-polymerisation modification

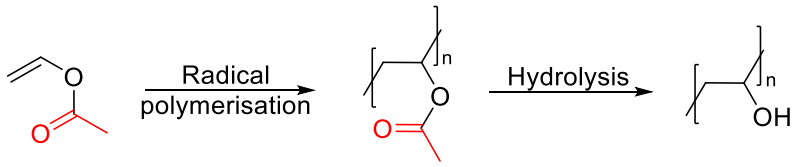
Polymers are essential to our lives, supporting advances in material development for everyday commodity and speciality applications including plastics in different uses, water-purification, textiles, pharmaceuticals, medical devices, oil and energy.[1] However, the polymer market is always seeking new polymers with better properties for different applications or modifying the existing to meet the new requirements. New polymer synthesis requires either new compatible catalysts, to initiate and control polymerisation, or novel monomer structures with desired functional groups.[2] Tremendous progress has been made in the last three decades in the development of new polymerisation methods to afford new polymer structures. These include living/controlled radical polymerisation,[3-5] olefin metathesis polymerisation,[6] stereospecific catalytic polymerisation,[7-8] late-transition-metal catalysis for olefin insertion polymerisation,[9-11] organo-catalysis for ring-opening polymerisation,[12] enzymatic polymerisation,[13-14] and supramolecular polymerisation.[15] These new methods have provided unprecedented opportunities for the design of new generations of polymeric materials with an increased level of complexity, functional properties and structural precision. Despite these improvements, there is still a broad range of side-chain functionalities that cannot be introduced by direct polymerisation using any currently available controlled polymerisation techniques. Such functional groups have ligating properties, e.g., amine, hydroxy, and carbonyl may completely prevent controlled polymerisation or may participate in side-reactions that can lead to loss of control over the polymerisation reaction.[16] For example, the direct polymerisation of epoxide monomers bearing primary amino groups is not feasible, since the nucleophilic amine can attack the epoxide ring and inhibits the polymerisation. Hence, Koyama *et al.* overcame this issue by thiol-ene coupling of 2- aminoethanethiol to the allylic groups of a pre-made polyether (Scheme 1.1).[17] Thus, this primary amino group expands the application of polyethers by permitting conjugation of biomolecules or low molecular weight compounds with polyethers.



(1.1) (1.2)

Scheme 1.1 Post-polymerisation modification of poly(allyl glycidyl ether)-co-poly(ethylene glycol) with 2-aminoethanethiol.[17]

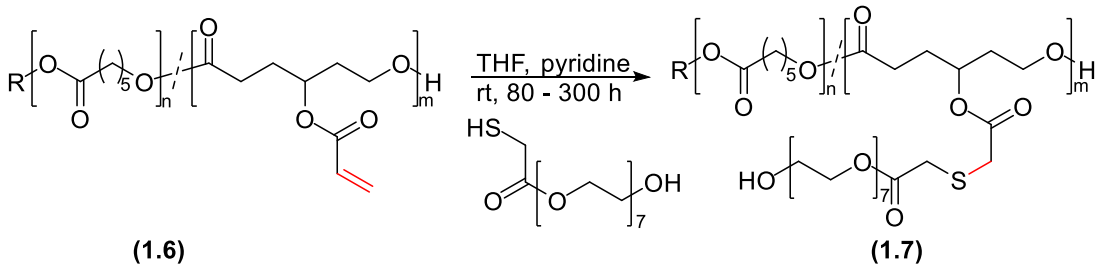
Another example is polyvinyl alcohol (PVA) which also cannot be made directly from vinyl alcohol (VA) because VA is practically a very unstable enol form of acetaldehyde. Therefore, PVA is prepared by performing the hydrolysis of the precursor polymer, polyvinyl acetate (Scheme 1.2).[18]



(1.3) (1.4) (1.5)

Scheme 1.2 Preparation of PVA by hydrolyzing a premade polyvinyl acetate.

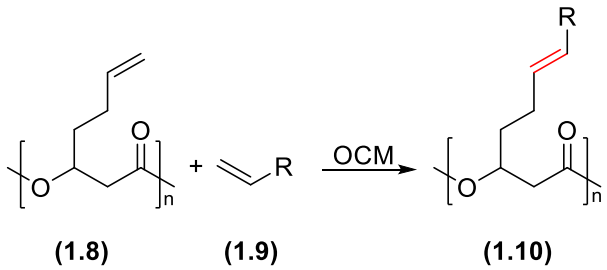
Hence, post-polymerisation modification is an alternative approach to overcome the limitations of conventional polymerisation methods.[2] It is based on the polymerisation of monomers with difunctional groups; one is compatible with the selected polymerisation method and the other group is either inert towards the polymerisation conditions or protected but allows a quantitative conversion in a subsequent reaction step. Thus, diverse libraries of functional polymers with the same average degrees of polymerisation but variable side chain functionality may easily be generated. Among several groups, olefins are one of the most versatile groups for post-polymerisation modification. This functionality has proved useful as no protection or deprotection steps are needed to yield the functional polymer. Also, the versatility of the alkene group allows for a wide range of functionalisations to be performed, for example through Michael addition, radical thiol-ene addition, and epoxidation reactions.[2] The conditions of these reactions are mild enough to be applicable even on biodegradable polymers. Jérôme *et al.* modified poly(ε-caprolactone) (PCL) by Michael-type addition to synthesise an amphiphilic PCL and no degradation was observed.[19]



Scheme 1.3 Coupling poly (ε-caprolactone-co-γ-acryloyloxy-ε-caprolactone) with PEG by Michael-type addition.

A poly(ethylene glycol) (PEG) chain was added on a copolymer contains double bonds distributed along polyester backbones of ε-caprolactone and γ-acryloyloxy-ε-caprolactone (Scheme 1.3).[19]

Another post-polymerisation modification method has attracted considerable attention recently and will be discussed in detail in this chapter is olefin cross-metathesis (OCM). OCM is a unique post-polymerisation modification technique comparing with the previous organic transformations due to the feature of preservation of the double bond post metathesis (Scheme 1.4).[20-22]



Scheme 1.4 A representative scheme of poly(hydroxyalkanoate) modification by olefin cross metathesis.[20]

All these post-polymerisation modification methods pave the way for many novel polymer structures and properties. However, the chemical modification is not the only way to modify the properties of polymers, the precise architectural control of polymer structure has also been a principal subject in polymer chemistry.

1.2 Polymer architecture and topology

The shape or topology of a polymer is one of the essential factors determining its properties and in turn influencing its applications.[23] One of the key elements crucial to the biological function of the human body's natural polymers, such as proteins,

polysaccharides and polynucleotides, is their unique three-dimensional (3D) structures. Given this fact, much effort has been spent to the development of efficient synthetic methods for accurate control of polymer with various architectures and topologies along with their structure-dependent properties. This includes linear-, cyclic, cyclo-, branched-, star-, helical-polymers, polycatenane, polyrotaxanes, (Figure 1.1), folding, dendrimers, cylindrical-, spherical-, etc.[24-25]

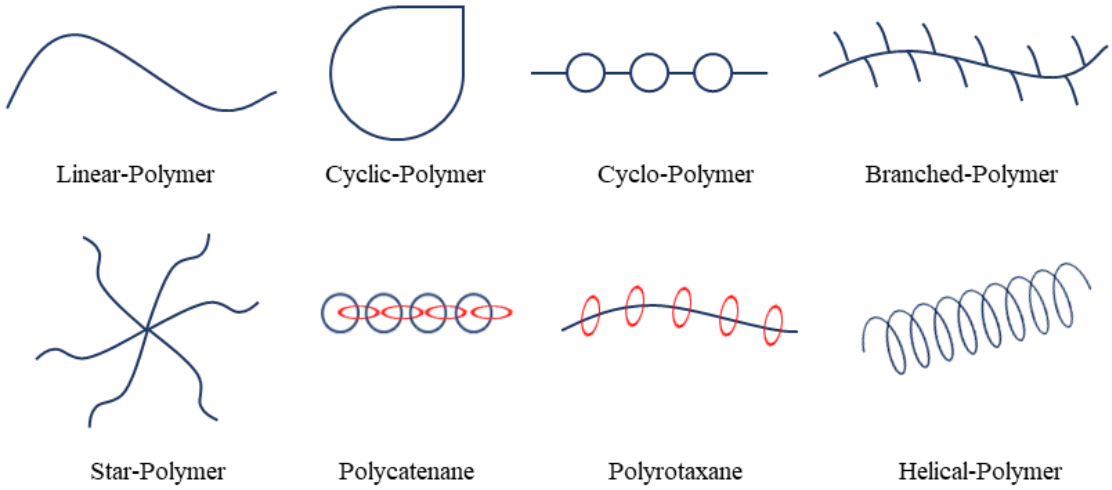


Figure 1.1 Representative the variety of polymer shapes.

Each of these structures can exhibit drastically different physical and functional properties even with having identical chemical compositions. For example, star polymers,[26-27] cyclic- polymers,[28-31] dendrimers[32] and hyperbranched polymers,[33] generally have a smaller hydrodynamic volume, less polymer entanglement in bulk and lower viscosity in solution compared with their linear counterparts. These properties can help to not only reduce the amount of solvent but also make the moulding process easy because of the low melt viscosity.[34-37] Additionally, it has been shown that cyclic-polymers have longer circulation half-lives than their linear structures making them better drug carriers for drug delivery applications.[38] In addition, the helical macromolecule attracts the interest of synthetic polymer scientists due to its unique conformation. Indeed, one of the critical factors crucial to the high penetration efficiencies of cell-penetrating peptides (CPPs) is their inherent helical structures.[39-41] For example, modified poly(arginine) mimics adopt a stable helical conformation was reported by Cheng *et al.* and exhibited superior helix-related cell-penetrating properties.[42] Also, noncharged hydrophilic helical poly(phenyl

isocyanide) (PPI) chains stretched out from spherical micelles was developed by Wu *et al.* exhibited faster cell membrane permeability than that of normal ones with random linear chain coatings.[43-44] The spatial arrangement of the atoms in a polymer chain can also play an essential role in the polymer 3D structure. For example, amylose and cellulose are both cyclopolymers of cyclic glucose units. The main difference is the anomeric configuration; while amylose's glucose units are linked with α(1→4) glycosidic bond, cellulose's monomeric units are linked by β(1→4) glycosidic bond. This difference in bonding causes amylose to form helical structures and cellulose to form straight polymer chains (Figure 1.2).[45]

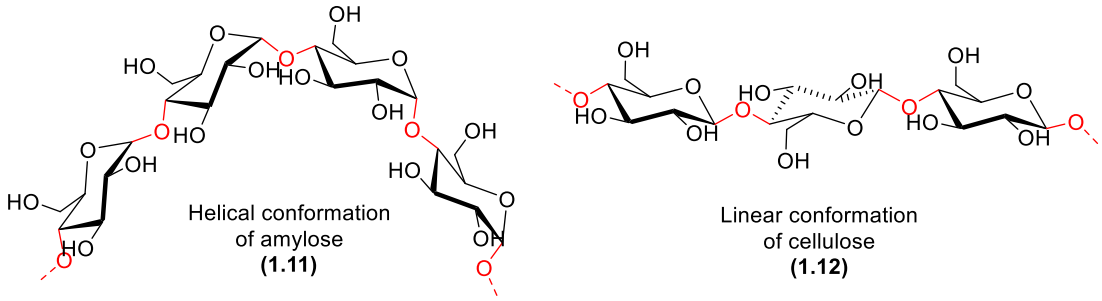


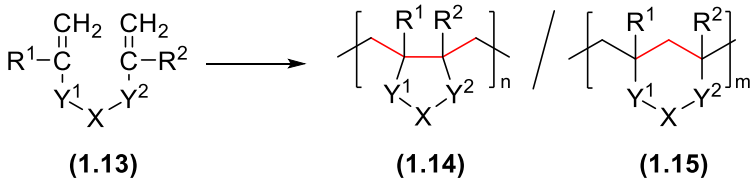
Figure 1.2 Representative the chemical and conformational structures of amylose and cellulose.

The synthetic cyclopolymers are of special interest now in both academic research and industrial applications since they mimic the natural polymers. Cyclopolymers bearing heteroatom functional groups are of much interest and importance, as they may show improved beneficial properties compared to the linear polymers.[46]

1.3 Stereocontrolled cyclopolymers

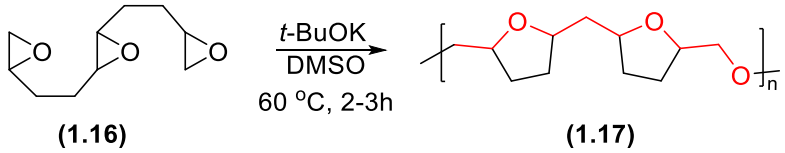
Cyclopolymers, by definition, are linear polymers consisting of in-chain cyclic structures. This kind of polymer has attracted attention due to their unique properties and potential functions.[46-48] The topic has been widely covered by a review published recently by Takeuchi *et al.*[46] For synthesising of such polymers, cyclopolymerisation of bifunctional monomers is a direct and convenient method. The two reactive groups in the monomers are polymerised through alternating reactions of intermolecular addition and intramolecular cyclising addition.[49-50] This strategy can afford varied functionalised cyclopolymers with different rings sizes. However, the bifunctional monomers need to be designed accurately to overcome the difficulty of the

thermodynamically stable ring formations. This polymerisation can be activated using radical, ionic, or transition-metal mediated chain-growth mechanisms.[46] The two functionalities are covalently linked by a bond(s), which can be properly designed to build the chemical elements of the polymer backbone during the synthesis and, in some cases, be modified by post-polymerisation modifications.[51] The two functionalities can be either identical or having different reactivities toward the polymerisation mechanism involved. Up to now, various nonconjugated dienes or divinyl compounds have been employed providing sp^3-sp^3 C-C main chain cyclopolymers. For example, cyclopolymers with five- and/or six-membered cyclic units have been afforded by the cyclopolymerisation of 1,5-hexadiene and 1,6-heptadiene with early transition metal complexes including Ti, Zr, and Hf (Scheme 1.5).[53-55]



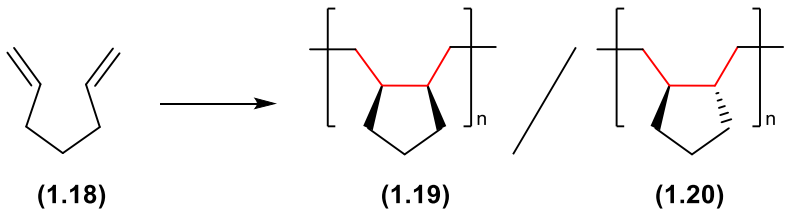
Scheme 1.5 Cyclopolymerisation of nonconjugated dienes of divinyl monomers.

Other examples include radical or ionic cyclopolymerisation of difunctional styrenic compounds,[56] di(meth)acrylates,[57] divinyl ethers,[58] diisocyanides,[59] and *bis*(acrylamide).[60] Cyclopolymerisation involving double cyclisation, ring-opening, or isomerisation have also been developed, generating unique repeating units, which can hardly be obtained by conventional polymerisation methods (Scheme 1.6).[63]



Scheme 1.6 Double cyclisation polymerisation of 1,2:5,6:9,10-triepoxydecane (**1.16**).[63]

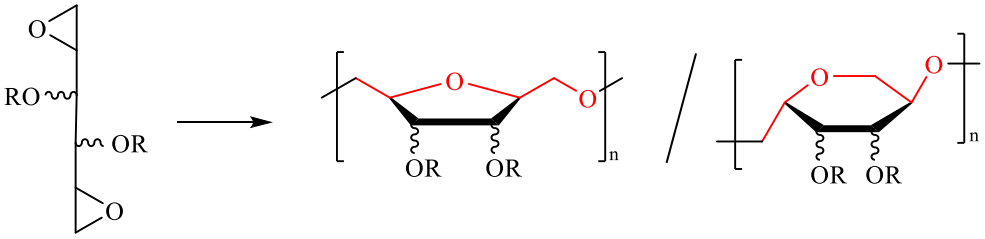
Particular emphasis was spent on the extent and origin of both stereo- and regioselectivity with the different initiator systems used. Recent advances in new initiating catalysts of late transition metals, such as Pd, Co, and Fe, enabled highly regio- and/or stereoselective cyclopolymerisation (Scheme 1.7).[61-62]



(1.18) (1.19) (1.20)

Scheme 1.7 Cyclopolymerisation of 1,6-heptadiene (**1.18**) to stereoselective five-membered ring cyclopolymers.

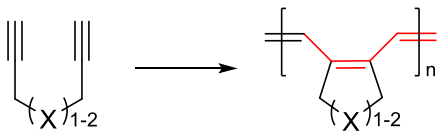
Diepoxides have been known to undergo cyclopolymerisation to give cyclopolyethers. The cyclopolymerisation of 1,2:5,6-dianhydrohexitols was proven to be a powerful method for the synthesis of polycarbohydrates. The stereochemistry of the diepoxides and the type of the polymerisation (cationic or anionic) significantly affects the structure of the repeating units of the synthesised polymer. The cationic or the anionic polymerisation of 1,2:5,6-dianhydro-3,4-di-*O*-alkyl-(D-mannitols) or other isomers (allitol) or (galactitol) affords a polymer with either five-membered or six-membered ring units in a highly regio and stereoselective manner (Scheme 1.8).[64-78]



(1.21) (1.22) (1.23)

Scheme 1.8 Cyclopolymerisation of diepoxide (**1.21**) to produce polycarbohydrates.

Moreover, the cyclopolymerisation of diynes is remarkable since the resulting polymers have π-conjugated structures on their backbones and interesting physical, electrical, and optical properties. Recent achievements in the cyclopolymerisation of α,ω-diynes by tailored Ru- and Mo-alkylidenes have been reported. Special emphasis was put on the stereo- and regioselectivity of different initiator systems. Recently, developed molybdenum imido alkylidene *N*-heterocyclic carbene (NHC) complexes allow for the cyclopolymerisation of α,ω-diynes bearing protic functional groups such as hydroxyls and carboxylic acids. The catalyst rivals Ru-alkylidenes both in terms of regio- and stereoselectivity and also in terms of activity and functional group tolerance (Scheme 1.9).[79-86]



(1.24) (1.25)

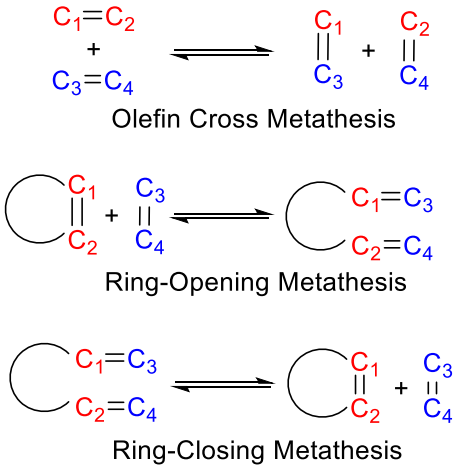
Scheme 1.9 Cyclopolymerisation of diynes monomer to π-conjugated cyclopolyenes.

Cyclopolymerisation of bifunctional monomers is the common route for obtaining cyclopolymers. However, olefin metathesis, a widely used reaction in organic chemistry, has also been used but rarely for making cyclopolymers.

1.4 Olefin metathesis

1.4.1 Introduction

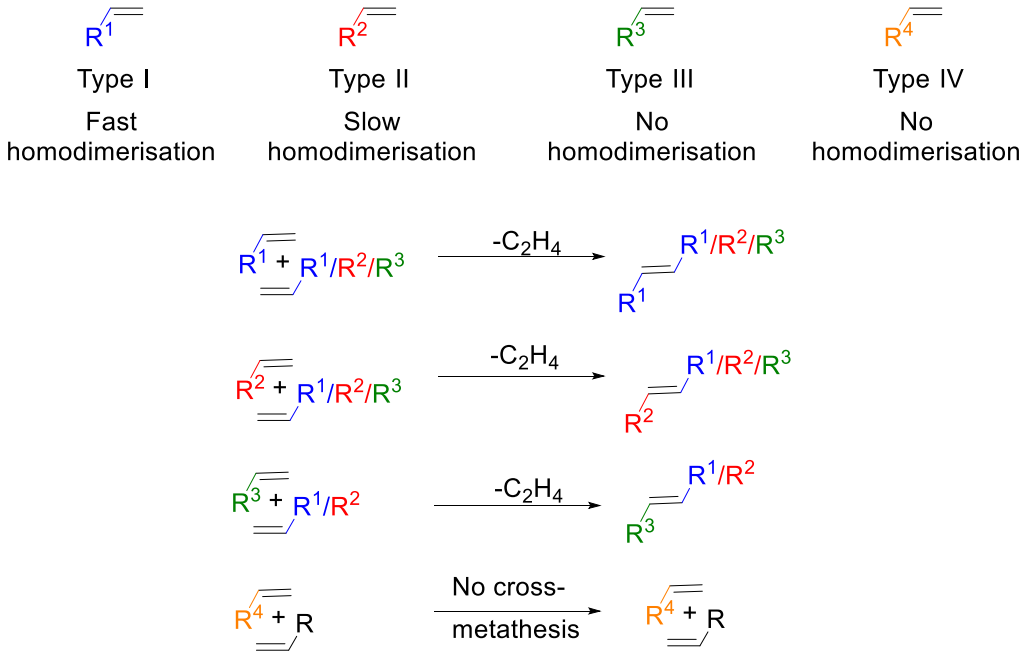
Olefin metathesis (OM) is one of the most powerful methods for the formation of carbon-carbon double bonds. In 2005, Yves Chauvin, Robert Grubbs and Richard Schrock received the Nobel Prize for their achievements in this field. Metathesis stems from the Greek meaning 'change of position, transposition' of two olefin bonds, generating two new ones.[87-88] Generally, olefin metathesis can be classified into three main categories: cross, ring-opening and ring-closing metathesis (Scheme 1.10).[89] Further types of OM reactions are derived from these classes and will be mentioned later.



Scheme 1.10 Different types of olefin metathesis; cross metathesis, ring-closing metathesis and ring-opening metathesis.

As shown in (Scheme 1.10), with an appropriate metathesis catalyst, olefin cross metathesis (OCM) can transpose C_1=C_2 and C_3=C_4 into C_1=C_3 and C_2=C_4. This type

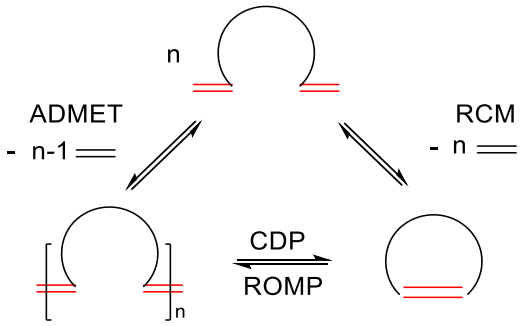
of reactions is mechanistically complex and controlling such transformations can be difficult because the catalyst must react and link two different olefin cross partners; otherwise, homodimerisation dominates.[90] Another type is ring-opening metathesis (ROM) through which a cyclic olefin reacts with a linear olefin, generating an acyclic diene. The driving force is the release of ring strain; this also ensures minimal reaction back to the cyclic compound.[91] Finally and the most widely used is ring-closing metathesis (RCM). In this transformation, two-terminal alkenes react with the help of a catalyst to generate a cyclic olefin, with the release of a smaller olefin C_3=C_4.[92] The most important aspect of olefin metathesis reactions is the reaction either does not generate a by-product or only produce one, such as ethylene, which can be removed by evaporation. However, some olefins are easy to prepare; terminal and some di-substituted alkenes, while tri- or tetra-substituted olefins present a challenge due to higher levels of steric hindrance and complications associated with controlling stereochemistry.[87] Selectivity can be a challenge when the metathesis reaction occurs between two chemically different alkenes. For this reason, Grubbs devised an experimental model to aid in the design of selective OCM reactions.[90] The model classified alkenes into four different types based on their ability to homodimerise and the ability of those homodimers to engage in a secondary OCM reaction (Scheme 1.11). These are derived from the steric and the electronic influence of the alkenes. The ease of homodimerisation decreases as the steric bulk surrounding the alkene increases. Furthermore, electron-rich alkenes are more reactive compared to electron-deficient alkenes. Generally, sterically unhindered and electron-rich alkenes can be classified as type I alkenes, whereas sterically hindered and electron-deficient alkenes can be categorised as type IV alkenes, with a gradient of reactivity existing in between these extremes. Type I alkenes undergo fast homodimerisation, and the homodimers formed are readily able to react in a secondary metathesis reaction. Type II alkenes undergo slow homodimerisation and the homodimers formed are unlikely to participate in a secondary metathesis reaction. Type III alkenes are unable to homodimerise but can couple with alkenes of type I or II. Lastly, type IV alkenes cannot participate in OCM at all but do not interfere with catalyst activity towards other alkenes.[93]



Scheme 1.11 Alkene categorisation of Grubbs's model into type I, type II, type III or type IV.

1.4.2 Ring-closing metathesis

RCM is as an efficient strategy in organic synthesis, and it has been greatly used in the preparation of a wide spectrum of complex molecules with many functionalities. It produces unsaturated small, medium or macro rings by the intramolecular metathesis of two terminal alkenes to form the cycloalkene as *E*- or *Z*- isomers.[92] The driving force for the cyclisation refers to entropic favourability of formation of two molecules per one molecule of the starting material. Also, the reaction is driven by the evolution of a small molecule, ethylene in most cases, and pushed to completion.[94] The product formation is greatly influenced by the reaction conditions. High dilutions are required to minimise intermolecular cross-linking and promote intramolecular RCM.



Scheme 1.12 Equilibria relate all olefin species: acyclic diene metathesis (ADMET), ring-closing metathesis (RCM), ring-opening metathesis polymerisation (ROMP) and cyclodepolymerisation (CDP).

If the reaction mixture is too concentrated, OCM will occur promoting acyclic diene metathesis (ADMET) polymerisation and through its extensive cross-linking (Scheme 1.12). Thus, the synthetic efficiency of RCM is restricted due to the reaction equilibria and competition between intramolecular ring-closing and intermolecular reactions.[92] The challenge when operating under such an equilibrium lies in identifying the various factors that could be applied to maximise RCM. Conrad *et al.* reported RCM of some diene esters. In Figure 1.3, they monitored by matrix-assisted laser desorption/ionisation (MALDI) technique that ADMET oligomers (intermolecular addition) formed 51% of the initial products as kinetic products and then decreased gradually over the time, while the thermodynamic ring-closing product increased overtime to reach 99% on extended reaction times.[95]

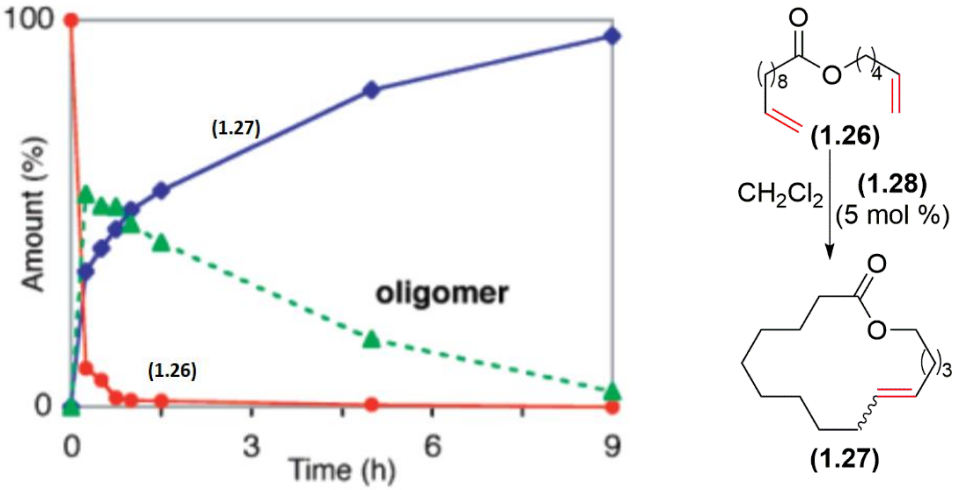


Figure 1.3 This kinetic graph was taken from Conrad *et al.* 2007 work[95] showing the RCM reaction conversion rate.

The formation of highly strained four-membered rings is thermodynamically unfavourable. However, five-, six- or seven-membered rings are readily achieved through RCM. RCM of medium (8-11 membered rings) and large rings (≥12) is more challenging. The formation of large rings is difficult as the probability of two olefins meeting to form a ring is lower for longer pendent chains.[92] Moreover, the required dilution for a specific ring size is often strongly dependent on the substituents. Forbes *et al.* reported systems in which ring closure was favoured by the Thorpe-Ingold effect, and thus possible without solvent.[96] In general, among many cyclisation reactions, RCM has gained enormous popularity in recent years as a tool to make many challenging rings. The mechanism for transition metal-catalysed olefin metathesis has

been widely studied over the past four decades. RCM follows a similar mechanistic pathway as other olefin metathesis reactions. The catalytic cycle includes an initiation phase by generating the active complex and then a propagation phase when the active complex promotes additional cycles.[97]

1.4.3 Olefin metathesis catalysts

All olefin metathesis reactions involve the association of the metal with an olefin substrate. There are numerous catalytic systems available for metathesis reactions.[98] Original catalysts used for metathesis were based on metals includeding on tungsten, rhenium, and osmium but these exhibit low stability and/or reactivity and have not been as extensively investigated.[98-99] However, the well-defined and commercially available molybdenum (Mo) complex and ruthenium (Ru) systems (Figure 1.4) are more commonly used.

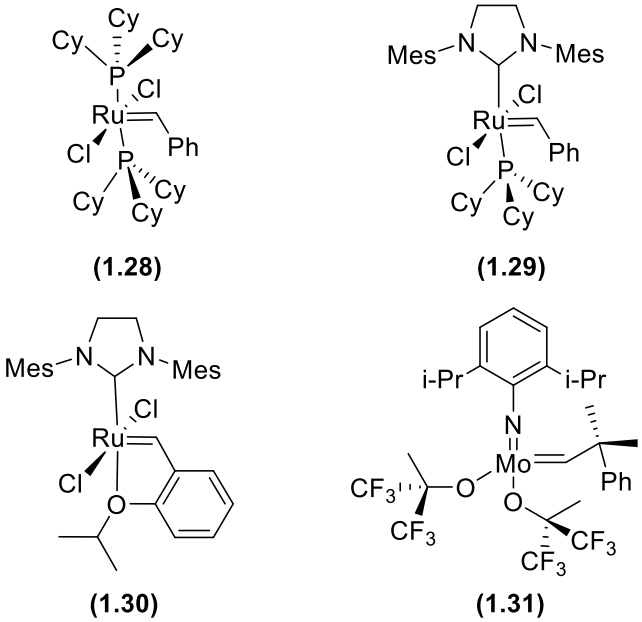


Figure 1.4 Representative the most common olefin metathesis catalysts.

Schrock's Mo catalyst **(1.31)**, prepared and handled under an inert atmosphere, is generally more active than Ru catalysts, which are stable to air and moisture. The activity of Mo and Ru catalysts are arguably complementary. Ru catalysts can be used with substrates which are functionalised with an alcohol, a carboxylic acid, or an

aldehyde. However, it can be inactive in the presence of structurally exposed amines and phosphines, but the reverse holds for Mo catalysts. The drawbacks of Mo-based carbene complexes are its high sensitivity to air, moisture or even to trace impurities present in solvents, cost of preparation, thermal instability on storage, and moderate to poor functional group tolerance.[98] On the other hand, Ru-carbene systems have drawn a lot of attention for many reason. First, they exhibit high reactivity in a variety of ROM, RCM and cross-metathesis processes under mild conditions. Second, they are remarkably tolerant towards many different organic functional groups. Lastly, their catalytic activity is not as sensitive as the Mo-carbene systems and so it is not significantly reduced in the presence of air, moisture or minor impurities.[98-100] However, the catalytic activity and lifetime are dependent on the used solvent.[101] Furthermore, the choice of catalyst is also key in predicting reactivity. For example, an alkene can be classified as a Type II alkene when reacting with Grubbs first-generation catalyst **(1.28)** but may alternatively be classified as a Type I alkene in the presence of Hoveyda–Grubbs 2nd catalyst **(1.30)**.[90] However, Grubbs's alkene classification model, alongside the aforementioned development of more active metathesis catalysts, now paves the way for the application of OM reactions to more complex systems, including polymers.

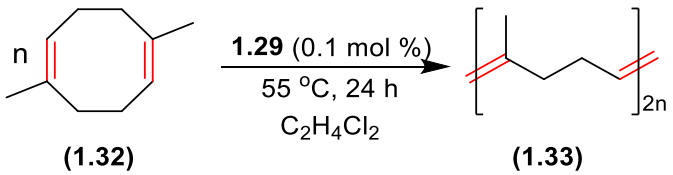
1.4.4 Olefin metathesis in polymer chemistry

1.4.4.1 In polymerisation

Olefin metathesis reactions have been developed extensively not only with small molecules synthesis but also in various polymerisation techniques. This includes;

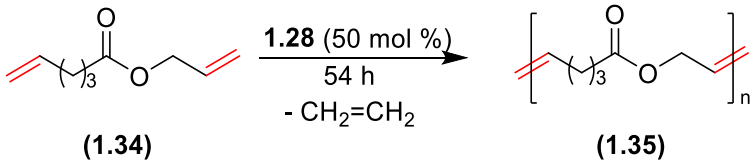
1- Cyclopolymerisation that has been mentioned above (Scheme 1.9).[102]

2- Ring-Opening Metathesis Polymerisation (ROMP) (Scheme 1.13) when the driving force of the reaction is relief of ring strain in cyclic olefins.[103]



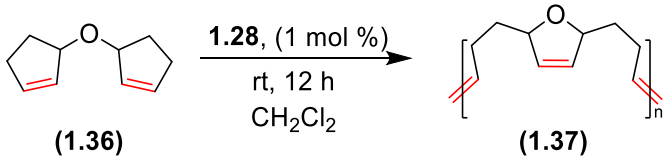
Scheme 1.13 Synthesis of ethylene-propylene copolymer by ROMP of 1,5-dimethyl-1,5-cyclooctadiene.

3- Acyclic diene metathesis (ADMET) polymerisation (Scheme 1.14)[104-105] which is driven by the release of volatile ethylene gas.



Scheme 1.14 Acyclic diene metathesis polymerisation of allyl hex-5-enoate.

4- Tandem polymerisation, which is a combination of two transformations; such as ring-opening/ring-closing metathesis (RO/RCM) (Scheme 1.15).[106-107]



Scheme 1.15 Tandem RO/RCM polymerisation of (**1.36)** to (**1.37**) polymer.

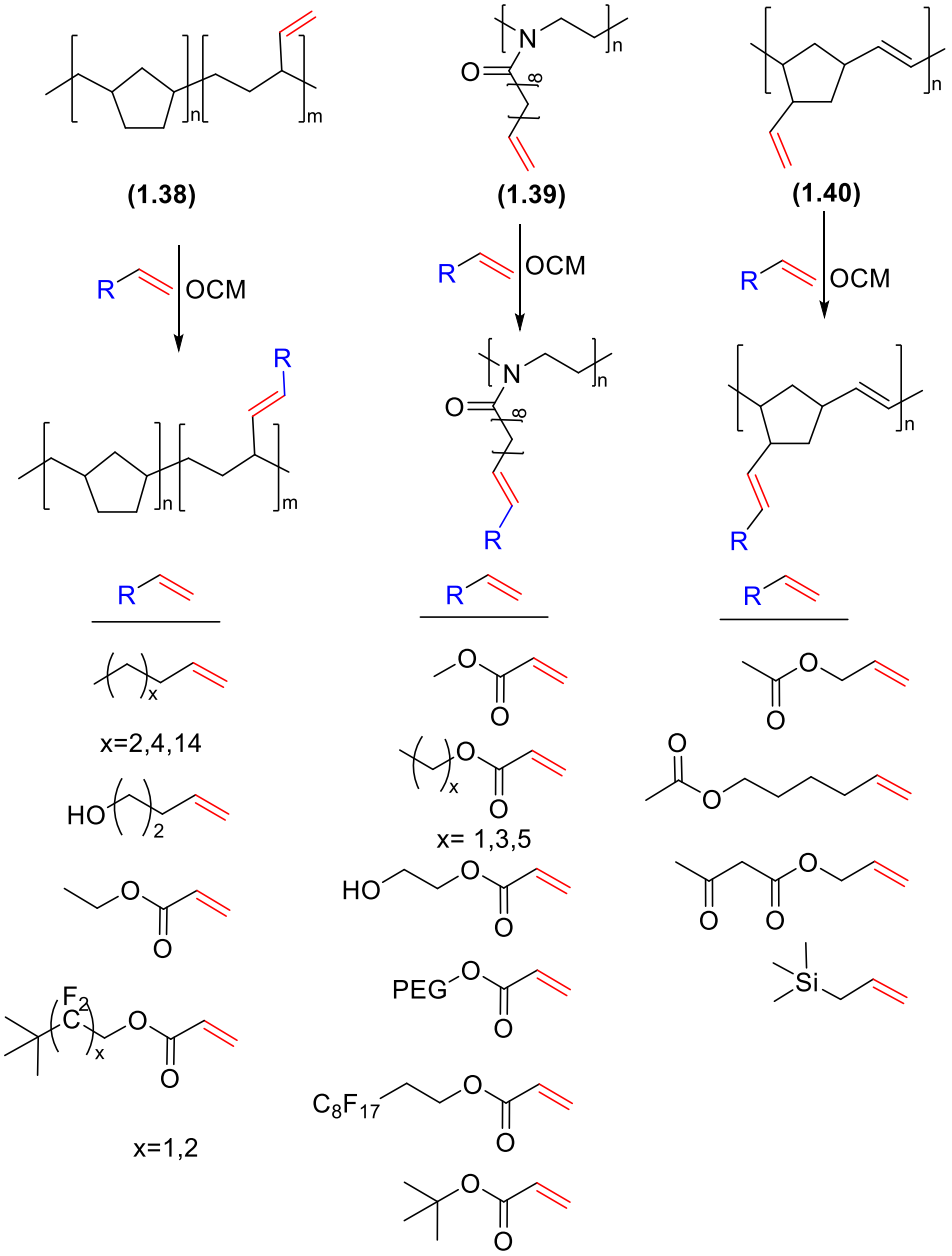
Olefin metathesis polymerisation opened the door to obtaining polyene polymers with different functional groups and reactive alkenes in the main chain, high molecular weight and narrow dispersity. This topic has been extensively covered in many reviews.[104,108] However, the use of olefin metathesis in post-polymerisation modification is still limited and has been reviewed by us recently.[93]

1.4.4.2 In post-polymerisation modification

1.4.4.2.1 Olefin cross metathesis

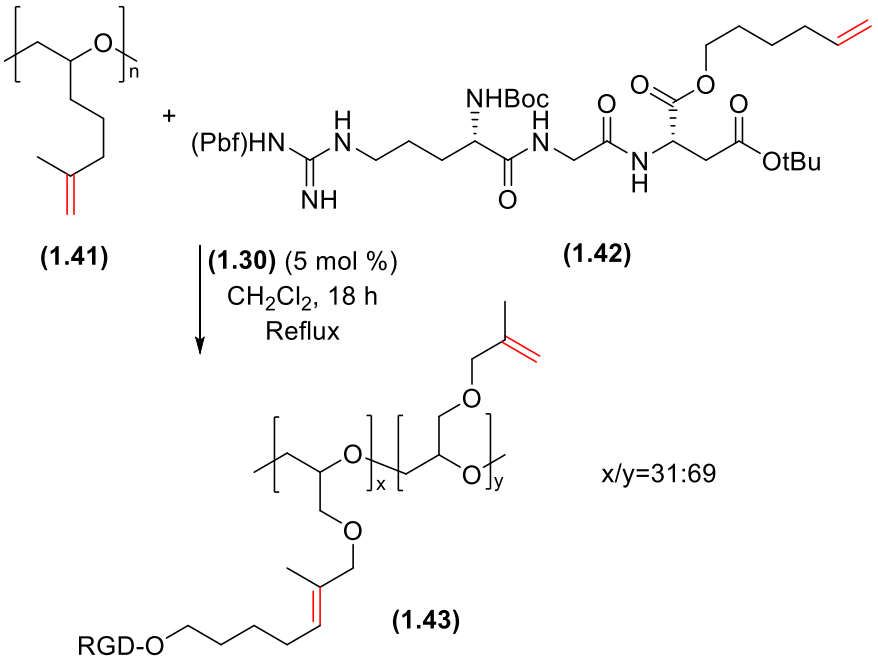
The use of olefin cross metathesis (OCM) in preparing functional polymers, by post-polymerisation functionalisation, is of growing importance.[93] The broad functional group tolerance of olefin metathesis offers a wealth of opportunities for inserting a wide range of functional groups into the polymer backbone, tuning its properties and expanding potential applications (Scheme 1.16). Up to now, a few polymers were functionalised by OCM starting in 2004 from polyolefins (**1.38**),[109] poly(2-oxazoline) (**1.39**),[110] poly(5-vinyl-2-norbornene) (**1.40**),[111] polyesters,[22] poly(β-heptenolactone)[20] and polyethers.[21] A wide range of alkene cross-partners with different functionalities was readily incorporated into these polymers to alter the thermal and chemical properties of the resulting polymers.[20-22] This strategy altered the glass transition

temperature (T_g) of the polymer, where the T_g temperature was increased substantially.[20,22,109,110] It can also affect the crystallinity of the polymer by changing the intramolecular bonding occurring between polymer chains.[20]



Scheme 1.16 Post-polymerisation olefin cross-metathesis. From left to right the work of Coates, Hoogenboom, and Zedník.[109-111]

Not only small cross partners were used in cross metathesis polymer-modification, but successful polyether-peptide coupling with 85% yield was also reported recently by Prunet *et al.* using poly(methallyl glycidyl ether) p(MAGE) **(1.41)** and protected tripeptide (RGD) **(1.42)** (Scheme 1.17).[21]

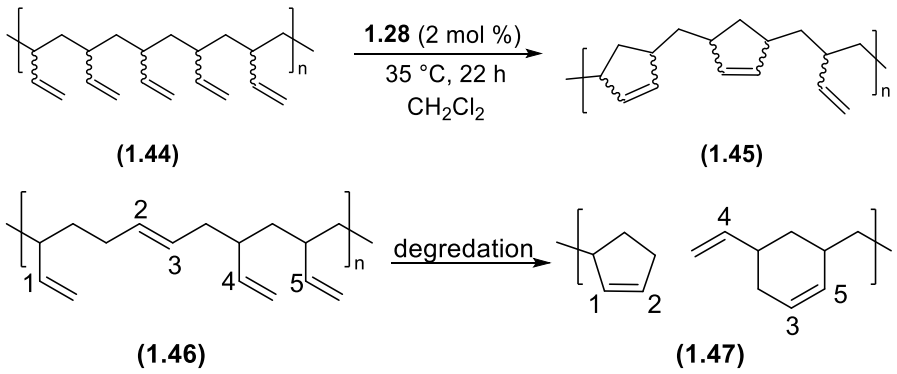


Scheme 1.17 Cross metathesis between p(MAGE) and protected RGD peptide.[21]

In general, solvent, type and quantity of the olefin cross-partner, concentration, temperature and catalyst type and concentration were all essential in optimising the reaction to yield the highest cross-metathesis/ self-metathesis ratio. Dilute conditions favour less self-metathesis, as the double bonds of the polymers are kept apart, although at the expense of catalyst reactivity.

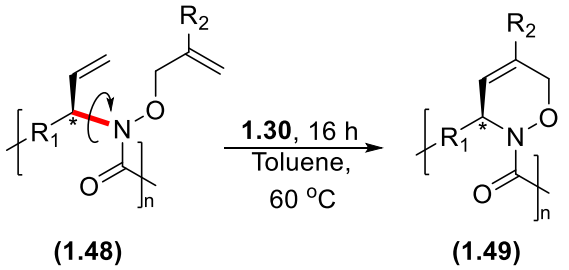
1.4.4.2.2 Ring-Closing Metathesis

As RCM produces rings, it targets modification of macrostructure rather than introduction of new functionality. The first example of using RCM in post-polymerisation modification was in 1996 when Coates and Grubbs made poly(cycloolefins) (**1.45**) by RCM of 1,2-polybutadiene (**1.44**). The pendent vinyl groups in the starting polymer are located along the polymer backbone and at suitable distances for cyclisation. Then, using metathesis catalysts (**1.28** and **1.31**) afforded a five-membered ring functionalisable cyclopolymer. On the other hand, if one of the olefin groups is located on the polymer backbone (**1.46**) the metathesis reaction could cleave the polymer chains (Scheme 1.18).[112]



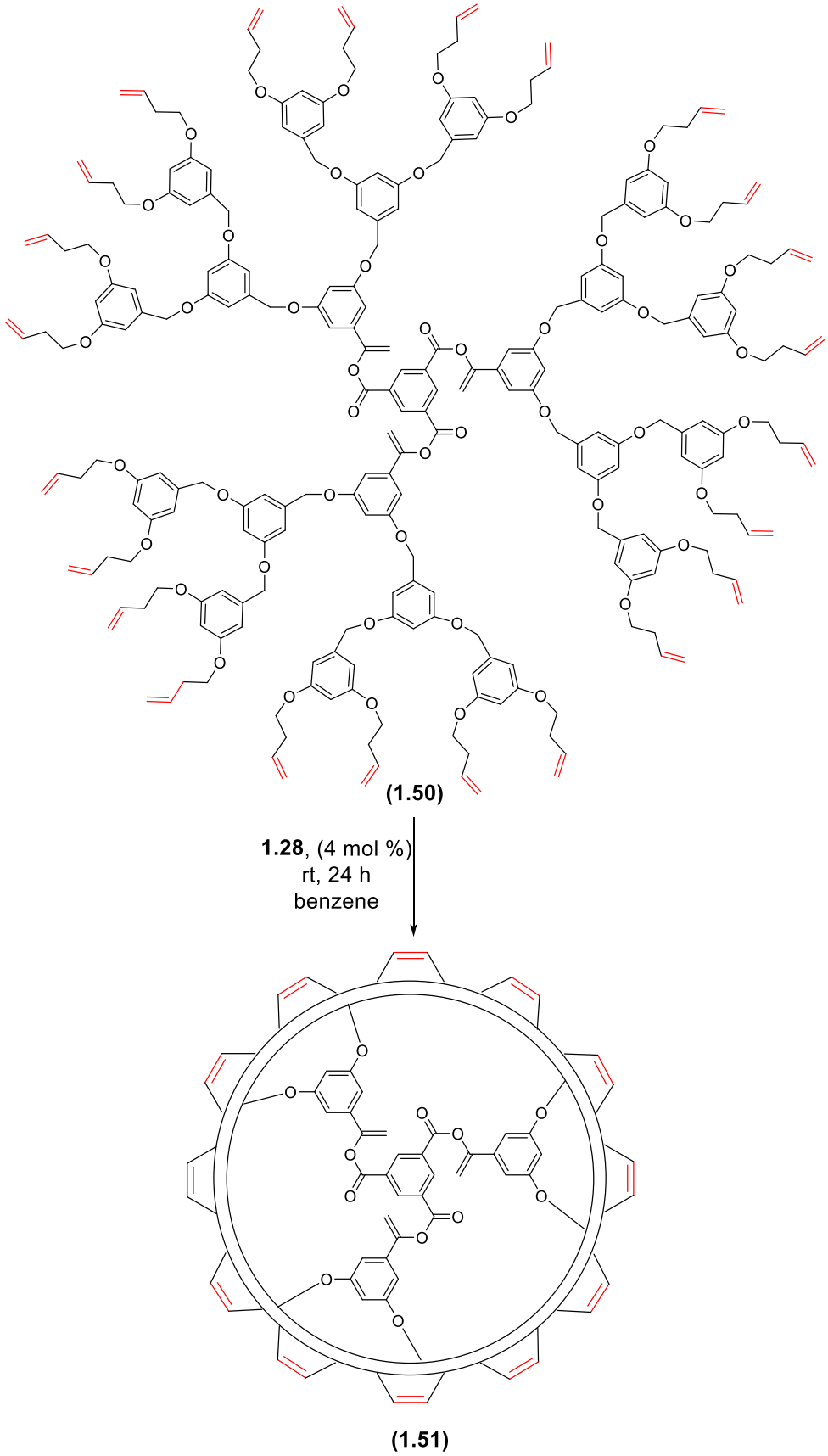
Scheme 1.18 Cyclisation of atactic 1,2-polybutadiene by RCM when the olefins in the polymer substituents (top) and metathetical degradation when an olefin exists in the polymer backbone (bottom).[112]

The second cyclopolymer was made by RCM in 2015 by Onitsuka *et al.* when they used metathesis reaction to produce a chiral cyclopolymer (**1.49** - Scheme 1.19). As RCM can restrict the conformation of the main chain, it can lock asymmetric centres to create a fixed chiral polymer, rather than a rotatable chiral chain. This conformational restriction led to a specific cyclopolymer structure which influences both physical properties and biological activity.[113]



Scheme 1.19 Ring-closing metathesis on a chiral linear polymer to generate a chiral cyclopolymer.

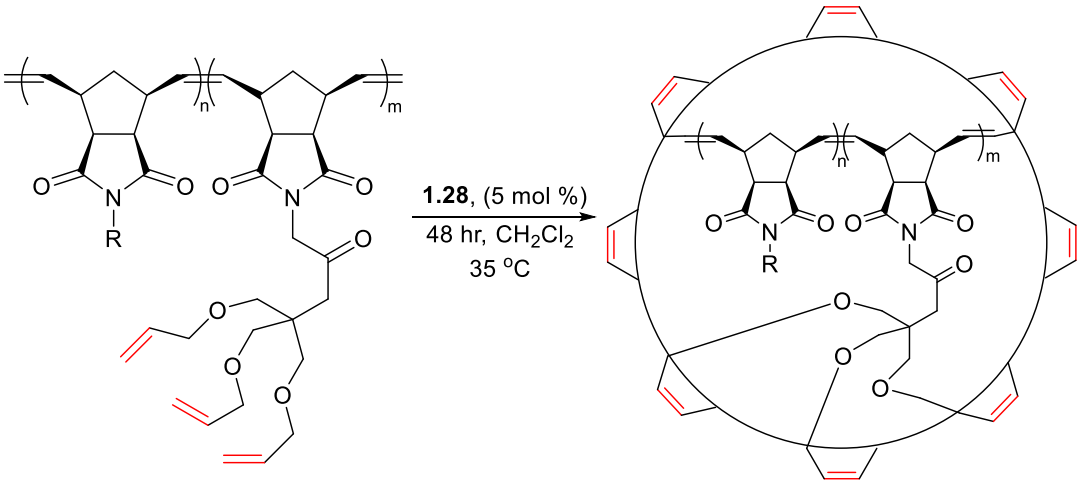
RCM also was used as a powerful technique in producing rings and capsules of varying sizes, properties and applications. Dendrimer formation and functionalisation by RCM led to many important applications including drug delivery agents,[114-115] molecular imprints,[116] and covalent organic nanotubes.[117] First successful RCM of a dendrimer was reported by Zimmerman *et al.*(**1.50** - Scheme 1.20), which metathesised terminal homoallyl ether groups to generate a ring-closed structure.[114] Control of the reaction conditions was essential for achieving complete conversion and for achieving the desired structure.



Scheme 1.20 Ring-closing metathesis of dendrimers with a homoallyl ether terminal group.[114]

High concentrations promoted OCM between dendrimers, proved by higher molecular weights and dispersities. Conducting the reaction at low concentrations (**1.30**, 4 mol%, [dendrimer] < 10^{-5} M) favoured RCM exclusively. Increasing steric bulk around the terminal alkene also favoured RCM at higher concentrations, while compact catalysts with minimal bulk (catalyst **1.29**) afforded higher yields. Also, the higher thermal stability of catalyst **1.29** was beneficial to the reaction to allow for a secondary rearrangement of the dendrimers to form extensively intramolecular cross-linked structures.[118] The reversibility of olefin metathesis reactions, offered another tool for controlling the size and rigidity of the formed dendrimer. Increased reaction times resulted in a decrease in the hydrodynamic volume of the dendrimer to reach the most thermodynamically stable conformation. Theoretically, complete RCM should lead to a decrease by ethylene mass (per two-terminal olefin units) of the overall mass, but experimental molecular weight determinations suggest a much hydrodynamic size loss. Thus, the size of individual macromolecules or rings can be tuned by controlling the RCM reaction conditions.[119]

Moreover, the use of RCM was extended to the synthesis of polymeric nanoparticles. The best example of this feature is shown in Scheme 1.21, transforming the cross-linkable polymer (**1.52**) into defined nanoparticle (**1.53**).

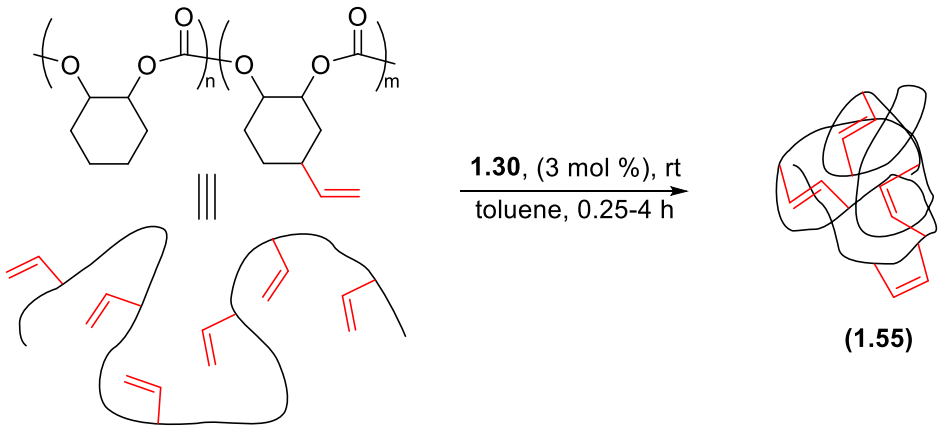


(1.52) **(1.53)**

Scheme 1.21 Synthesis of organic nanoparticles using ring-closing metathesis process.[123]

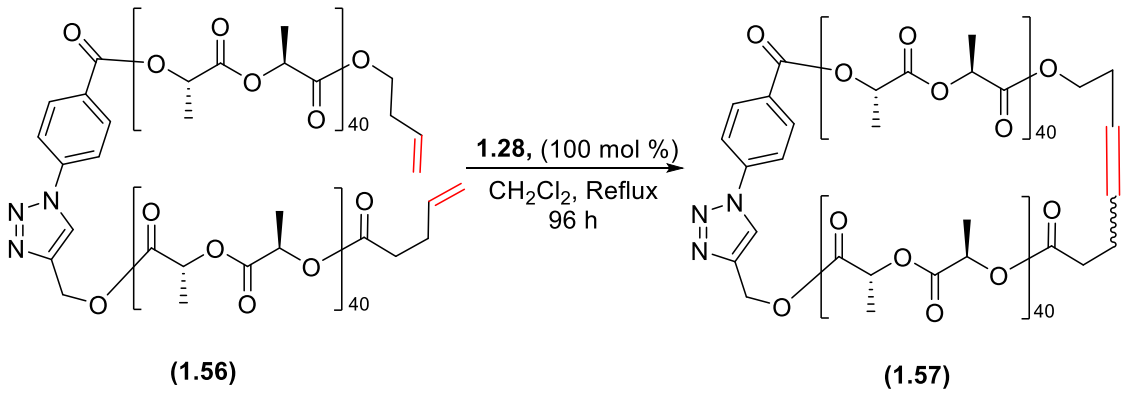
The degree of RCM conditions controlled the rigidity of the shell and the length of tether that shaped ring sizes, which could control both diffusion and guest/drug encapsulation.[120-122] The resulting olefin functionality was further functionalised by

post-RCM dihydroxylation to produce water-soluble nanoparticles of controlled size and shape.[123] Coates *et al.* investigated different RCM reaction conditions on a polycarbonate which has pendent olefin groups **(1.54)**, to observe different olefin metathesis reactions and analyse the outcomes *via* different characterisation techniques. At relatively high concentrations of polymer (>10 mg mL^{-1}), both RCM and OCM occurred. However, working at low concentrations (1 mg mL^{-1}), the apparent molecular weight decreased steadily, and the molecular weight distribution remained narrow, indicating that only RCM occurred. They found also a relationship between the hydrodynamic size and glass transition temperature (T_g) of products of an RCM reaction at various time periods. The results showed that when the reaction time and conversion increased, the T_g increased while the particle's hydrodynamic size decreased (Scheme 1.22).[124]



Scheme 1.22 Exclusive ring-closing metathesis on a vinyl functionalised polymer to produce nanoparticles.[124]

RCM has also acted as an effective tool in forming cyclic polymers (CPs). When the polymer chain termini are olefins groups, end-to-end linking reactions are a common route to generate CPs by RCM. However, this method is limited due to competing chain-extension reactions that are favoured with increasing chain length. A few CPs examples made by RCM were reported. Tezuka *et al.* made a cyclic amphiphile of polystyrene-*b*-poly(ethylene oxide) as a micelle which displayed a significantly enhanced thermal stability compared to its linear counterpart.[125] Also, cyclic poly(phosphoester) and cyclic stereoblock polylactides, which were both formed from RCM and could display better biological activity than their linear forms.[126-127]



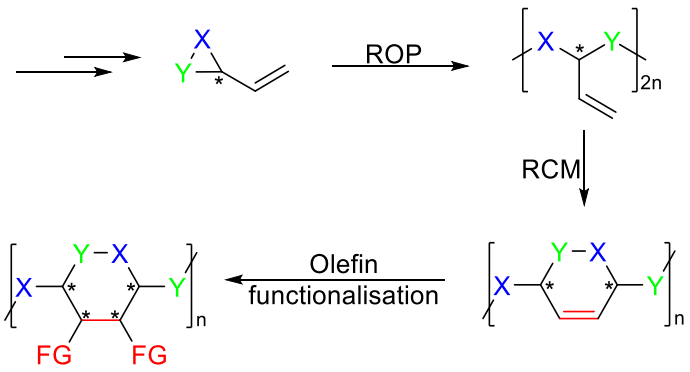
(1.56) (1.57)

Scheme 1.23 Synthetic scheme of cyclic stereoblock poly(lactide) acid by ring-closing metathesis.[127]

In general, the reaction conditions greatly influence product formation, and these include; concentration, temperature, length of the reaction, catalyst and olefin types. The most competitive reaction to the RCM reaction in macromolecules is OCM. High dilutions are required to limit intermolecular cross-linking and promote intramolecular RCM. Otherwise, OCM between the macromolecules will occur.

1.5 Aims and objectives

Historically, interest in chiral synthetic cyclopolymers has focused on mimicking natural polymers and controlling the absolute configuration of a synthetic polymer main chain. In addition, the use of RCM for making cyclopolymers is still limited. For these reasons, the aim of this work is preparing new stereocontrolled cyclopolymers by ring-closing metathesis as a post-polymerisation modification tool. To achieve this work, starting polymers with vinyl groups, located along the polymer backbone at ideal distances for cyclisation, are needed. Then, this work describes the design and synthesis of appropriate monomers, ring-opening polymerisation and post-polymerisation functionalisation. The stereogenic centre of the starting monomer determines the tacticity of the starting polymer and this in turn influences the conformation of the produced cyclopolymers (Scheme 1.24).



Scheme 1.24 Principle of preparing stereocontrolled functionalisable cyclopolymers by RCM.

Chapter two will explore this principle by describing the sysnthesis of cyclopolymers from an atactic and isotactic-rich starting polyethers. The conformations of the cyclopolyethers produced will be examined as it was hypothesised that the stereocontrolled ones would potentially have a helical conformation. Furthermore, a stereoselective functionalisation of the alkene of the resulting cyclopolyethers will also be explored.

In Chapter 3, the work will be extended to investigate the feasibility of synthesising different ring-sizes of cyclopolyethers by synthesising novel monomers and polymers are suitable for RCM. Chapter 4 will focus on expanding the work to polyesters by synthesising novel monomers and polymers that are suitable for RCM to obtain six-membered-ring functionalisable cyclopolyesters. Lastly, chapter 5 is a collaboration project about using different aluminium salen catalysts for regioselective polymerisation of L-thionolactide.

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Chapter 2. Stereocontrolled Functionalisable Cyclopolyethers

2.1 Polyethers

Aliphatic polyethers are non-degradable polymers, generated by ring-opening polymerisation (ROP) of epoxide monomers (oxiranes). Ethylene oxide (EO) and propylene oxide (PO) are the most used oxiranes among other substituted epoxide monomers. Poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) are a well-established and highly important class of polymers due to their uses in many different applications. The production scale is more than 33 million tons per year (Figure 2.1).[1]

PEO (2.1) PPO (2.2)

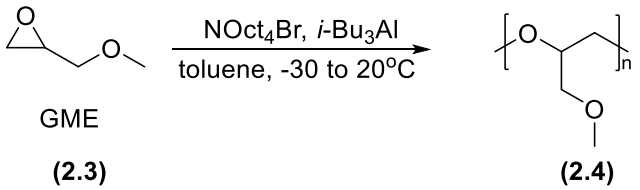
Figure 2.1 The chemical structures of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO).

PEO with low molecular weights (below 30 000 g/mol) is referred to as poly(ethylene glycol) (PEG). PEG is a crystalline thermoplastic polyether, and its aqueous solubility makes it unique among aliphatic polyethers that are commonly not water-soluble. PEG is used for a vast variety of water-based polymer applications, such as; dispersion stabilisation, laxatives, food additives. Superior blending, hygroscopicity, biocompatibility, very low immunogenicity, antigenicity and non-toxic properties of PEG have resulted in high demand for the pharmaceutical products such as tablets, ointments and other biomedical uses.[2-3] PEG is also widely employed for drug delivery purposes by conjugating of therapeutic peptides, proteins and liposomes to enhance blood circulation times.[4-5] This so-called "PEGylation" strategy relies on the "stealth properties" introduced by the attachment of PEG chains. PEGylated formulations typically experience decreased uptake by the macrophage system, decreased degradation by enzymes and reduced renal filtration.[6]

PPO, often designated poly(propylene glycol) (PPG) for lower molecular weights, is a non-water soluble and flexible polymer. PPO-based star polyether polyols exhibit

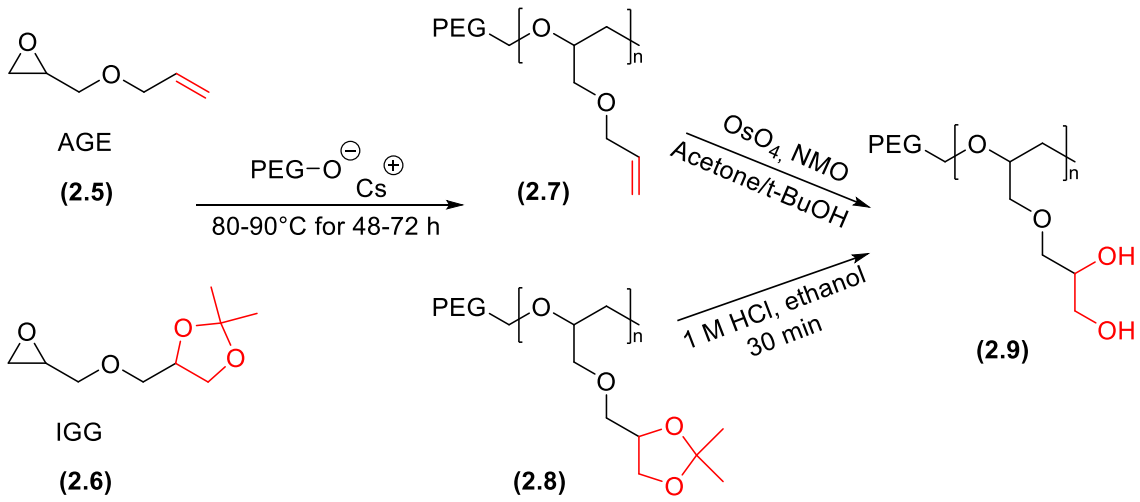
low glass transition and their amorphous nature make them play a key role in the synthesis of flexible polyurethane foams. Also, PPG is used for lubricants, antifoaming agents, softeners, rheology modifiers, and nonionic surfactants.[1,7]

To broaden the scope of applications for PEG and PPO, a broad range of chemical modifications can be introduced at these polyether's chains by three main strategies: (i) introduction of groups via a functional initiator (α- functionalization); (ii) use of a terminating agent containing a functional group (ω-functionalization); and (iii) "in-chain" functionalisation by copolymerisation with a functional epoxide.[1] The latter method, which plays an essential role in changing the physical and the chemical properties of the polyether backbone is desired for specific applications. The synthesis of functional homopolyethers can be conducted by polymerising the desired functionalised epoxide monomers which do not frustrate the polymerisation method, such as glycidyl methyl ether (GME) (Scheme 2.1).[8]



Scheme 2.1 ROP of GME. Methoxymethyl group of GME does not inhibit the polymerisation.

However, if the desired functional group would prevent the polymerisation, such as an hydroxyl or an amine, the desired functionalised polymer can be obtained by one of the following two methods. First, using protected functionalised epoxide monomers, which can be deprotected after the polymerisation to release the target functional group. Second, by using functionalised epoxide monomers which can be further functionalised after the polymerisation to the desired functional group. For example, the introduction of two vicinal hydroxyl groups per monomer unit has been realised by employing two different methods (Scheme 2.2). In the first approach allyl glycidyl ether (AGE, **2.5**) was co-polymerised with PEG followed by the subsequent dihydroxylation of the olefin group with osmium tetroxide. In the second approach, 1,2-isopropylidene glyceryl glycidyl ether (IGG, **2.6**) was co-polymerised with PEG, and the acetonide group can easily be deprotected with diluted acid to release hydroxyl units.[9]



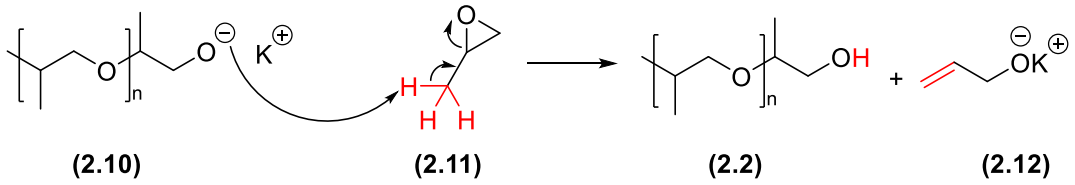
Scheme 2.2 Poly(ethylene oxide)-*b*-poly(glyceryl glycerol) preparation routes.

However, the latter method is not always favoured since these deprotection reactions are often accompanied by non-quantitative conversion[10] or require multi-step syntheses.[11] While some polyethers can be readily prepared by conventional polymerisation methods, others are more challenging to obtain due to the chemical nature of the starting epoxide monomers.

2.2 Epoxide polymerisation

The driving force for the ring-opening polymerisation (ROP) is the release of the high ring strain of epoxides, which is on the order of 110-115 kJ/mol for ethylene oxide. Epoxide monomers can be polymerised in three main ways: (i) base-initiated (anionic), (ii) acid initiated (cationic), and (iii) coordination polymerisation.[1] Each method has various advantages and disadvantages, with no single consensus technique for all structures and compositions emerging. The cationic ring-opening polymerisation (CROP) is rarely used for the polymerisation of EO or PO due to the formation of large amounts of cyclic polyether by-products as a result of "backbiting" processes, i.e., intramolecular chain transfer.[12] On the other hand, the anionic ring-opening polymerisation (AROP) method is the oldest and the most widely used approach, which is based on nucleophiles as initiators. Alkali metal oxide compounds with high nucleophilicity are the most commonly employed for this purpose.[1,13] The counterion should exhibit low Lewis acidity and preferentially little or no interaction with the chain end. The polymerisation rate constants increase with increasing size of

the counterion ($Na^+<K^+<Cs^+$), as it can be derived from the hard and soft acid and base (HSAB) concept.[14,15] Increasing atomic radius of the counterion, which translates to increasing "softness" by decreasing affinity to the comparable "hard" oxygen atom. Potassium is the most commonly used due to reasonable polymerisation results and lower cost in comparison to caesium. However, AROP is highly sensitive to monomer structure and intolerant of many chemical functionalities, which can result in limitations in terms of polymer architectures and long polymerisation times. Substituted epoxides can exhibit tendencies toward chain transfer to monomer, resulting in decreased molecular weight control with different chain-end functionality.[1] For example, the AROP of propylene oxide is obstructed by the proton of the methyl group due to the high basicity of the initiator system. This causes extensive chain transfer to the PO monomer with an elimination reaction creates an allyl alkoxide (**2.12**) as a new initiator (Scheme 2.3). This results in low molecular weight PPO with an unsaturated allyl end group.[16]



(2.10) **(2.11)** **(2.2)** **(2.12)**

Scheme 2.3 Molecular weight-limiting chain transfer to monomer and subsequent elimination reaction in AROP of PO.

For this reason, several catalytic ring-opening polymerisation approaches have been investigated. Among these, N-heterocyclic carbenes (NHCs) (**2.13** - Figure 2.2) as a catalyst system were used for ROP of EO and PO. Although this approach did not produce a high molecular weight of PPO (only 4500 g/mol), it generated the opportunity to obtain α,ω-functional PEG. The mechanism of polymerisation initiation is based on the formation of a zwitterionic species (imidazolium alkoxide) which in turn propagates the polymerisation.[17] However, in order to achieve high molecular weights (>50 kg/mol), a greater selection of monomer substrates, and isotactically enriched materials, several other alternative pathways to polyethers have been introduced in the last two decades. One of these routes is using phosphazene bases that belong to the neutral Brönsted "super" bases family, which are highly basic but weakly nucleophilic. This metal-free polymerisation technique relies on the use of

phosphazene bases as deprotonation or complexation agents. After deprotonation, the bulky phosphazenium cation, such as 1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethyl-amino) phosphoranylidenamino]-2λ5, 4λ5 - catenadi(phosphazene) (**2.14** - Figure 2.2) represents a soft counterion with a low tendency for the on-pair association.[18] Consequently, high polymerisation rates in nonpolar solvents under mild reaction temperatures can be observed, as the chain end is highly reactive. This system permits the synthesis of not only a wide range of poly-substituted oxiranes but also unprecedented and "challenging" block copolymer pairs with polyether blocks, such as vinyl polymer-based block copolymers (polystyrene, polyimide, polybutadiene, polyvinylpyrrolidone) with polyether in a one-pot reaction with no need for isolation or purification after individual synthetic steps.[1,19-21]

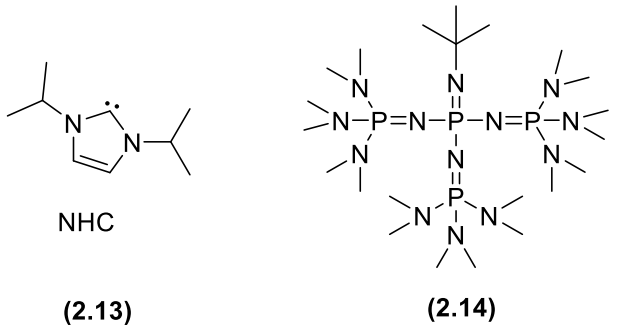
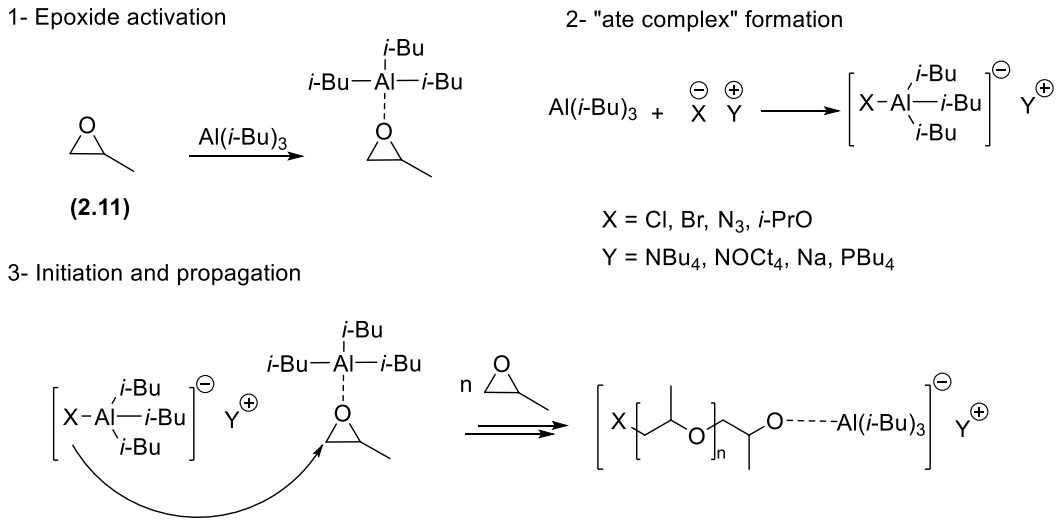


Figure 2.2 N-Heterocyclic Carbenes (NHCs) (**2.13**) and Phosphazene bases (**2.14**) are used for epoxide polymerisation.

Lastly, coordination polymerisation, sometimes also called "anionic coordination polymerisation", is the second most commonly used method after AROP. Here, the catalysts consist of an organometallic compound with an active metal-heteroatom (Mt-X) bond. The metal may be Al, Zn, or Cd, and X = O, Cl, or N. The coordination of the epoxide has two main effects: (i) activation of the monomer for the polymerisation, and (ii) generation of specific orientation of the reacting monomers to afford stereospecific polymerisation.[22] Also, coordination polymerisation with the monomer activation system results from the interaction of a Lewis acid with the oxygen of the epoxide ring. This decreases the electron density in the epoxide ring, thereby facilitating subsequent ring-opening (Scheme 2.4). The initiation proceeds through the formation of an "ate complex" between the Lewis acid (catalyst) and a weak nucleophile (initiating species) (Scheme 2.4).[23-28] With this approach, it has been

possible to obtain different copolymers of EO and PO with several substituted epoxides and high molecular weight M_n exceeding the 30 000 g/mol limit.[29-33]



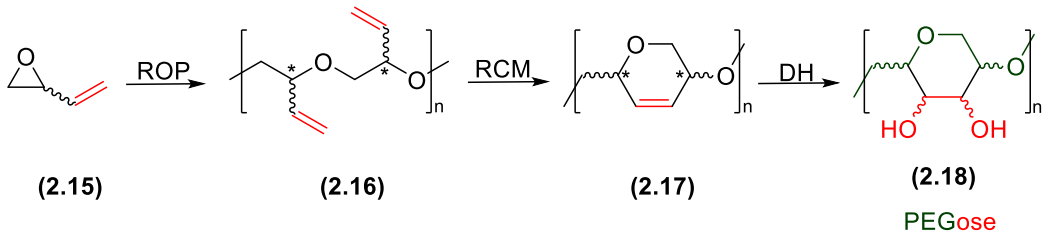
Scheme 2.4 Reaction mechanism of the "activated monomer" technique, exemplified for the polymerisation of propylene oxide (PO).[19]

These alternative strategies overcome the limitations of AROP for PO and other substituted epoxide monomers. However, AROP is still the favoured option, in particular when the polyethers are made for pharmaceutical, biomedical and cosmetic applications. Alkoxide initiators with nontoxic metal ions (Na and K) exhibited excellent control over molecular weights and dispersities. For all other strategies, convenient removal of activating groups before use, regardless of whether a metal- or organo-catalyst has been used, remains a challenge, and sometimes it is mandatory due to the toxicity of the respective metal residuals. Thus, although the AROP technique dates back in the 1930s, this method is still superior to all other controlled or living polymerisation techniques for key biomedical applications.[1]

2.3 Aims and objectives

Besides functionalised linear polyethers, several stereo- and non-stereocontrolled cyclopolyethers have been synthesised by either ring-opening polymerisation,[34] cyclopolymerisation[35] or tandem RO/RCM polymerisation.[36] Coates and Grubbs initiated investigations on polymeric substrates containing suitably-spaced olefins to prepare five-membered rings of cycloolefin polymers via RCM.[37] For this reason, this chapter aims to extend this principle to polyether backbone to afford a new family of

cyclopolyethers. To the best of our knowledge cyclopolyethers made of dihydropyran cyclic units have not been reported yet. The presence of an alkene group in the cyclic units make these types of polymer functionalisable by post-polymerisation modification. Furthermore, functionalisable stereocontrolled cyclopolyethers made of a 1,4-linked six-membered ring had also not been obtained before the date of this work. Poly(epoxybutene) (PEB) (**2.16**) is an excellent platform for functionalisable cyclopolyethers (FCPE) (**2.17**) by RCM since the distance between its olefin groups is ideal for cyclisation. The produced cyclopolyethers from PEB would be made of 1,4-linked six-membered dihydropyran monomer units. The conformations of the resulting cyclopolyethers can be controlled by controlling the tacticity of the starting polymers (PEB). In addition, this ring contains an olefin group which makes the polymer functionalisable to afford a wide range of functionalised cyclopolyethers (Scheme 2.5). Dihydroxylation (DH), in particular, is our main interest to obtain a novel polymer family encompassing a poly(ethylene glycol) backbone and sugar-like functionalities "PEGose" (**2.18**).

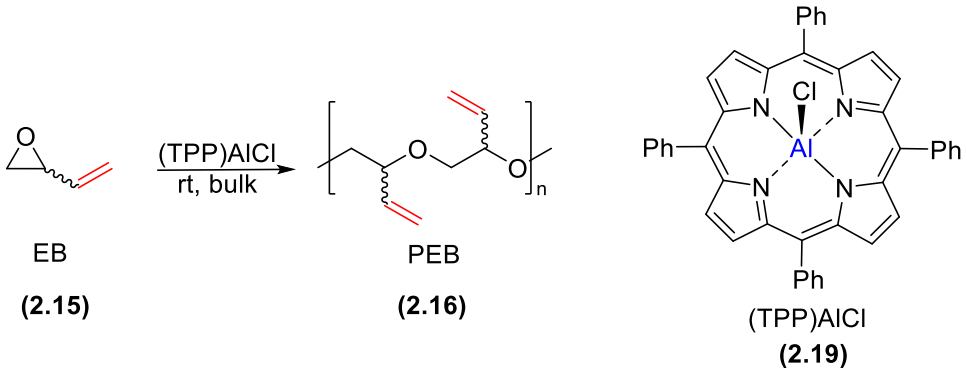


Scheme 2.5 Schematic reactions present the aim of this chapter by ROP of epoxy butene (**2.15**) to afford PEB (**2.16**). RCM of PEB to FCPE (**2.17**) and the alkene group of FCPE can be dihydroxylated to PEGose (**2.18**).

2.4 Ring-opening polymerisation of 3,4-epoxy-1-butene

3,4-Epoxy-1-butene (EB) (**2.15**), as a functional oxirane, has been homopolymerised a few times in the literature, using a bimetallic cobalt catalytic system.[38-40] The early attempts of ROP of EB using this cobalt catalytic system, a potassium *tert*-butoxide catalytic system or tetraoctylammonium bromide in the presence of triisobutylaluminum[41] led, unfortunately, to either incomplete conversion or yielded an insoluble material. However, when we used tetraphenylporphyrin aluminium

chloride [(TPP)AlCl] (**2.19**) as an initiator,[24-28,42] the results showed a controlled ROP of EB with a narrow dispersity (Scheme 2.6).



Scheme 2.6 ROP of 3,4-epoxy-1-butene (**2.15**) to afford PEB (**2.16**) using (TPP)AlCl (**2.19**) as an initiator.

Table 2.1: Ring-opening polymerisation of racemic 3,4-epoxy-1-butene (EB).

Entry	$[EB]_0:[A]_0:[B]_0$[a]	Time (days)	Con.(%)[b]	$M_{n,th}$[c]	M_n[d]	$Đ$[d]
1	36:1:0	2	>99	2560	3200	1.19
2	50:1:0	3	>99	3540	4400	1.18
3	70:1:0	5	96	4750	5400	1.17
4	100:1:0	7	90	6345	6550	1.19
5[e]	100:1:0	3	96	6765	3600	1.6
6	170:1:1	2	82	9670	4650	1.27

[a][EB]: 3,4-epoxy-1-butene, [A]: TPPAlCl initiator, [B]: MAlBP; [b] Determined by ^{1}H-NMR spectroscopy of polymer/monomer peaks integration of -CHO- peak; [c] M_n theoretical = M_w(monomer)× (%Con.) + M_w(HCl); [d] M_n and $Đ$ determined by GPC vs uncorrected PS standard. [e] Reaction run at 60 °C.

Samples with desired molecular weights of poly(epoxybutene) (PEB) and narrow dispersities ($Đ$ ~ 1.2) were prepared under optimised reaction conditions using [(TPP)AlCl] as an initiator at bulk, under nitrogen and at ambient temperature (Table 2.1, entries 1-4). At higher temperature (60 °C), the polymerisation rate was faster but with a higher polymer dispersity and lower molecular weight (Table 2.1, entry 5). However, no allyl isomerisation was observed at this temperature.[43] Another attempt to reduce the reaction time was by using monomer activation system by methylaluminum *bis*(2,4,6-tri-*tert*-butylphenolate) [MAlBP] as a bulky Lewis acid.[26] However, it was noticed from the gel permeation chromatography (GPC) data (Table 2.1 entry 6) and proton nuclear magnetic resonance (^{1}H-NMR) spectrum that a side

reaction occurred between MAlBP and (TPP)AlCl led to two new initiators.[44] For this reason, the molecular weight, in this case, was almost half the one expected and the MAlBP residues became the polymer's end groups (Figure 2.3). This was not noticed when (TPP)AlCl was used alone.

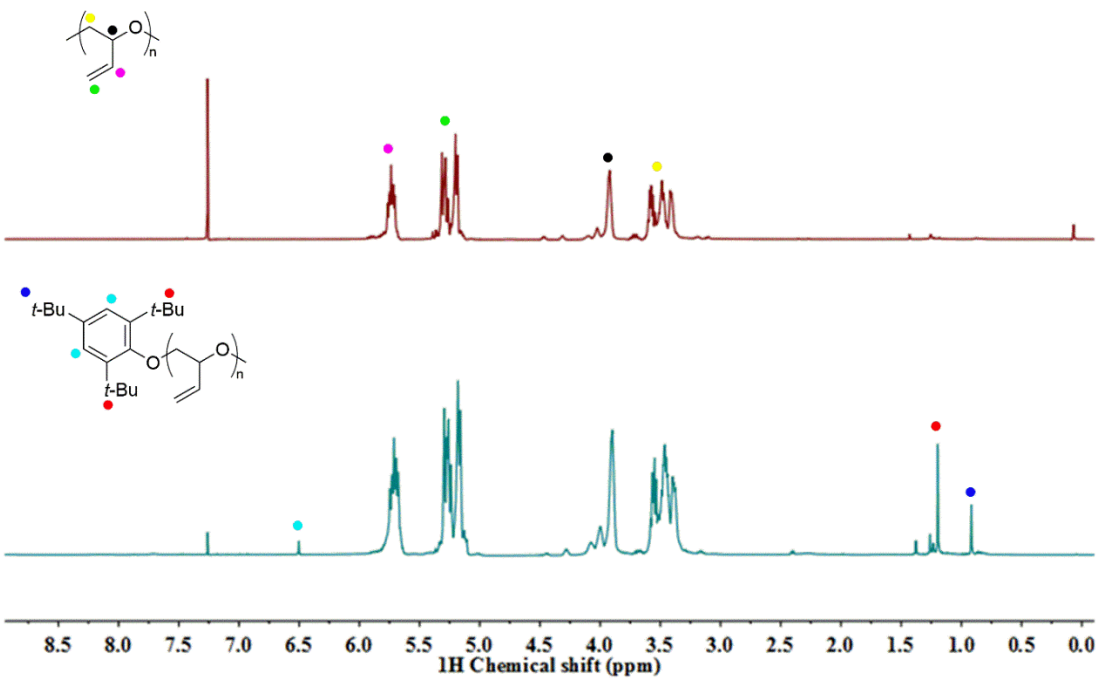
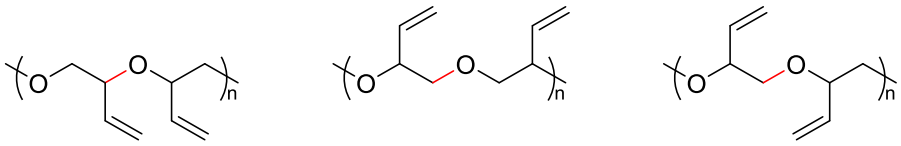


Figure 2.3 ^{1}H-NMR (*$CDCl_3$*, 500.2 MHz) of purified PEB prepared by (TPP)AlCl alone (top) and prepared by (TPP)AlCl and MAlBP (bottom).

Aluminium porphyrin catalysts showed controlled polymerisation resulting in exclusively head to tail (H-T) linkages with no appearance of head to head (H-H), or tail to tail (T-T), junctions (Figure 2.4).[45]



Tail to tail **(2.20)** | Head to head **(2.21)** | Head to tail **(2.22)**

Figure 2.4 Possible PEB structures.

However, the ^{13}C-NMR spectrum (Figure 2.5) of the resultant PEB showed two peaks for the stereogenic carbon, confirming the expected atacticity of the produced PEB (*a*-PEB), as the catalyst is not stereoselective.

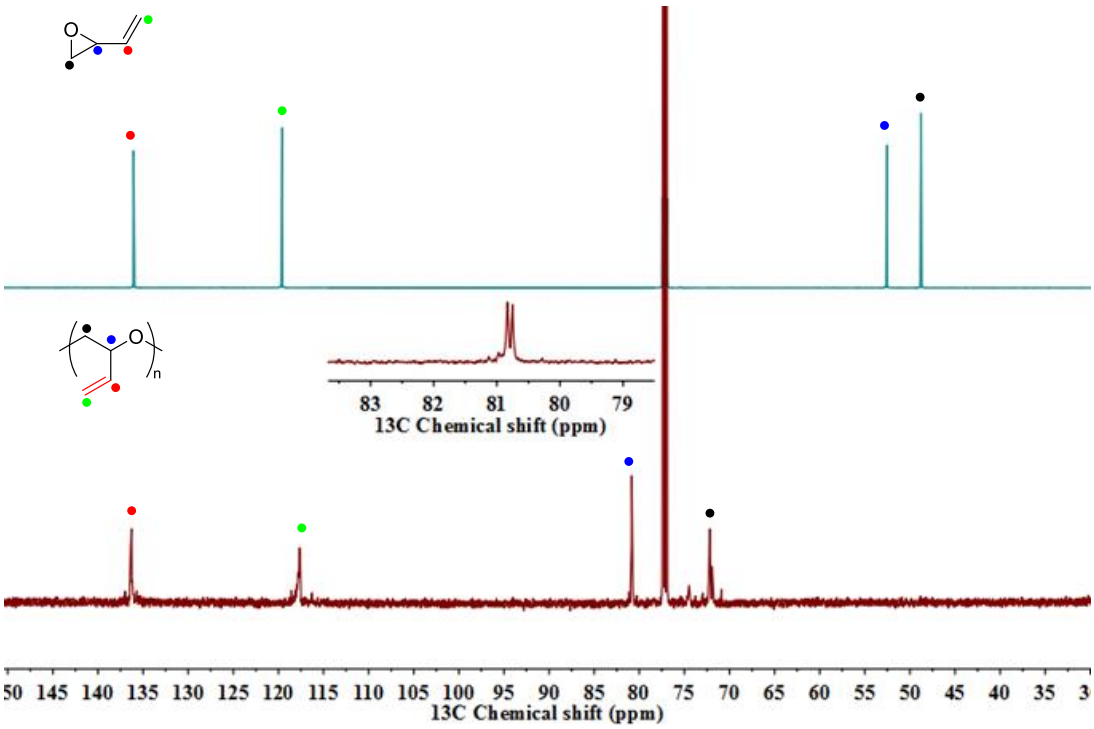
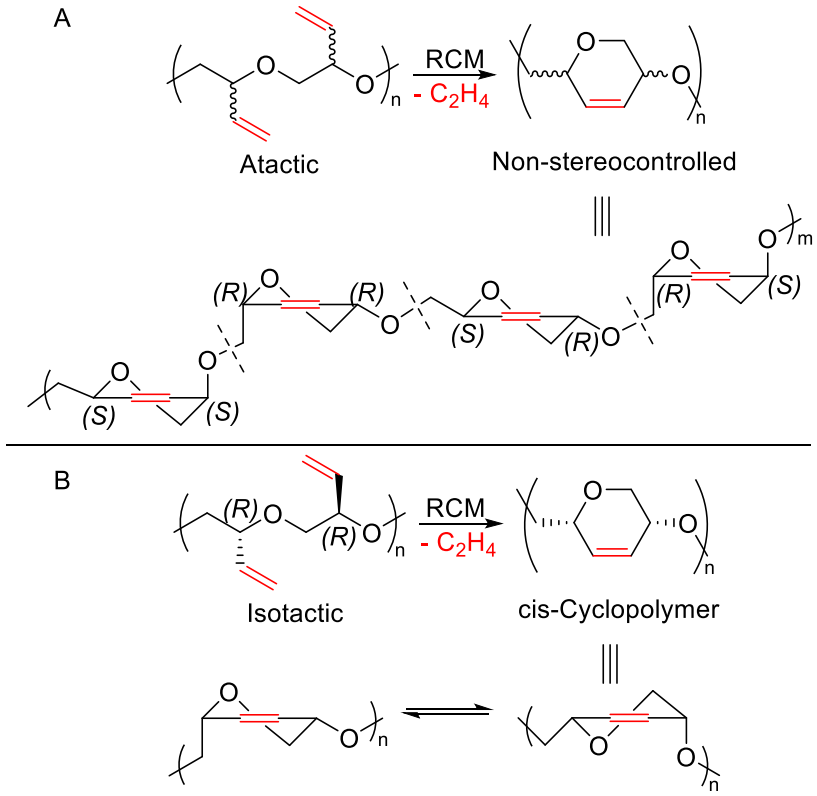


Figure 2.5 ^{13}C-NMR (*CDCl*$_3$, 125.8 MHz) of 3,4-epoxy-1-butene (**2.15**) (top) and (*a*)-PEB (**2.16**) (bottom).

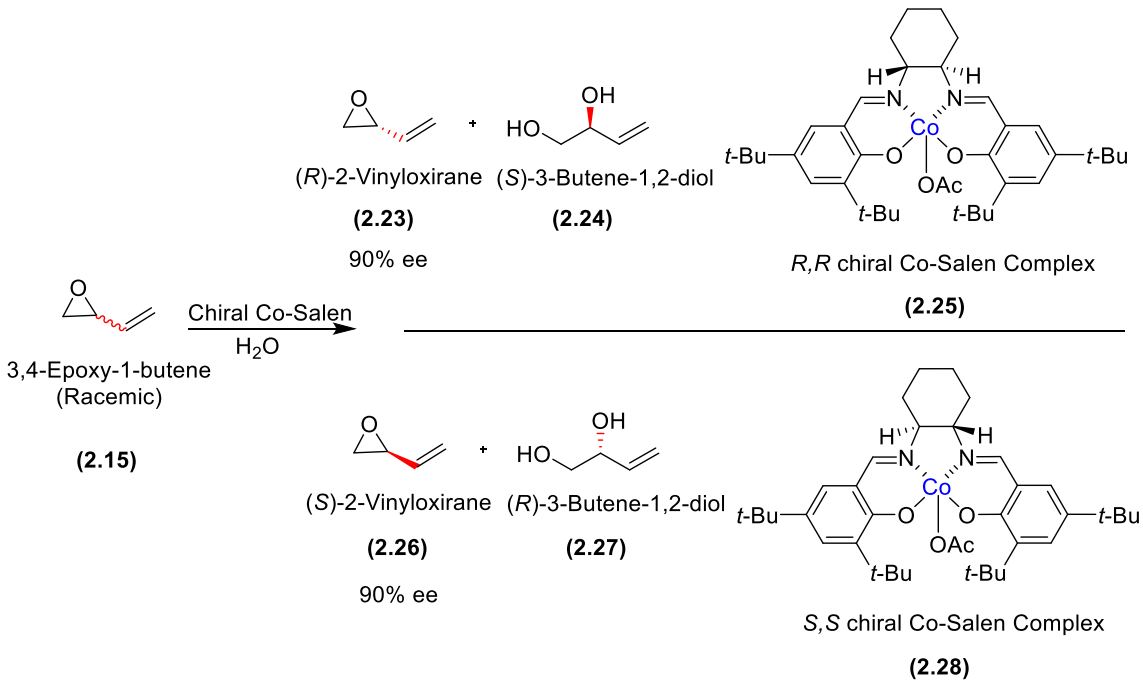


Scheme 2.7 Conformations of the produced cyclopolymers starting from atactic PEB (top) and from isotactic PEB (bottom).

RCM of (*a*)-PEB will not give a stereocontrolled cyclopolyether (Scheme 2.7 - A), and in turn this polymer will not be conformationally controlled. On the other hand, conformationally controlled structure can be obtained from the stereocontrolled derivative. Isotactic poly(epoxybutene) is easy to prepare and can lead to a stereocontrolled and conformationally controlled cyclopolyethers (Scheme 2.7 - B).

2.5 Preparing isotactic-rich poly(epoxybutene)

Isotactic-rich poly(epoxybutene) (*i*-PEB) can be made by either a stereoselective ROP of racemic EB or by ROP of enantiopure EB monomer. (*i*)-PEB with tacticity [mm] = 87.6 – 92.0 % was prepared using a bimetallic cobalt catalyst system developed by Coates *et al.*[38-40] Early attempts by the Shaver group using this catalyst system did not yield the desired polymer. For this reason, an enantioenriched monomer of EB was prepared using Jacobsen's hydrolytic kinetic resolution.[46] Chiral Co-Salen complexes gave 30-35% yield (60-70% theoretical yield) with around 95% enantiomeric ratio (er) (Scheme 2.8). ROP of the obtained enantioenriched monomer (**2.23**) *(R)*-EB, using the previous ROP optimum conditions, afford isotactic-rich poly(epoxybutene) *(R)*-PEB (**2.29**) shown in the ^{13}C-NMR spectrum (Figure 2.6).



Scheme 2.8 Enantioenriched monomers of EB (*R* and *S*) were prepared using Jacobsen's hydrolytic kinetic resolution.

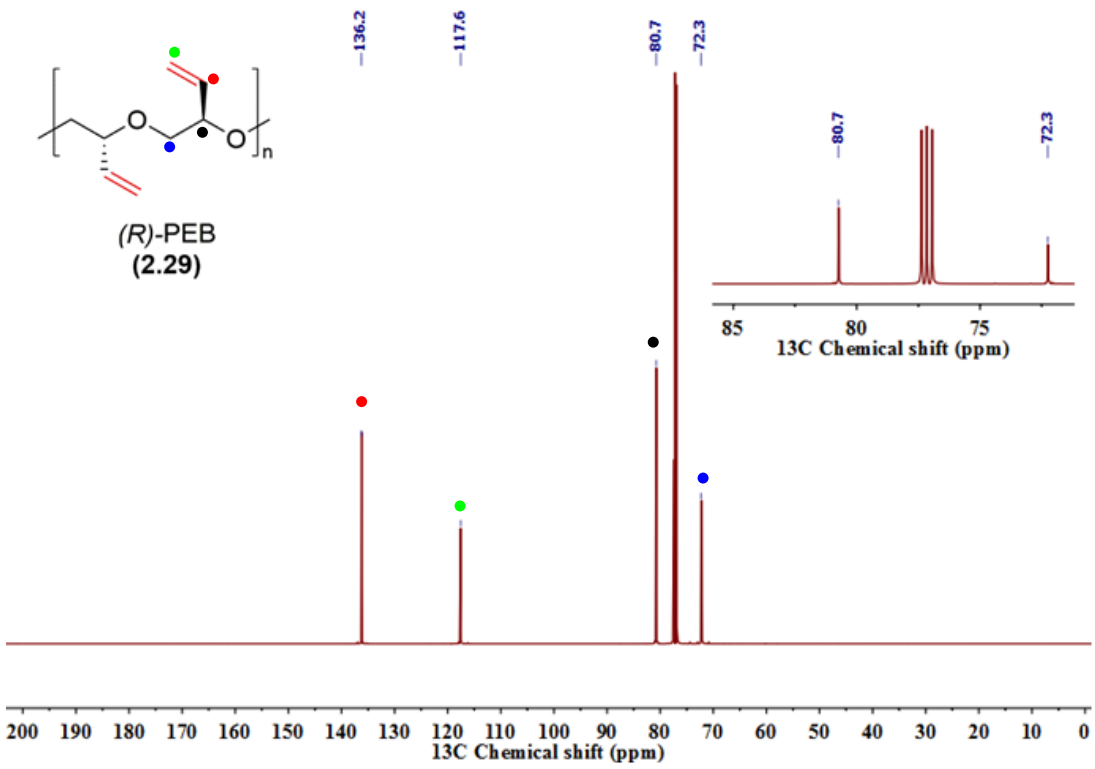
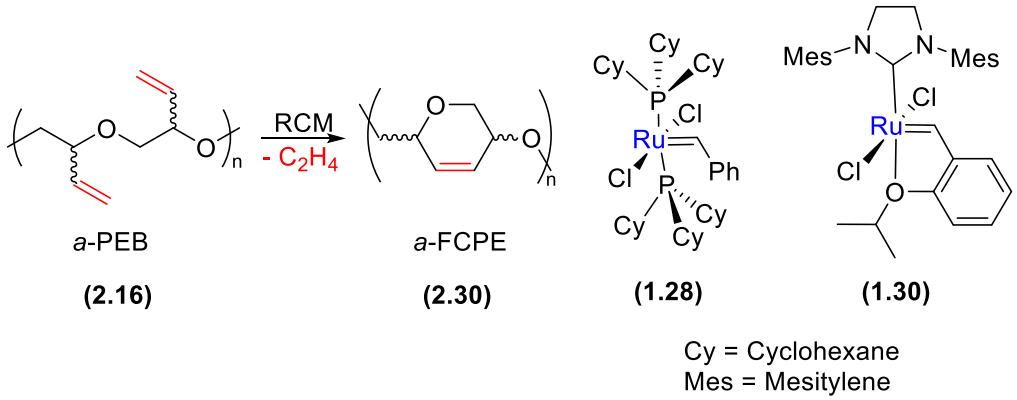


Figure 2.6 ^{13}C-NMR (*CDCl*$_3$, 125.8 MHz) of (*R*)-PEB (**2.29**) prepared from (*R*)-EB monomer (**2.23**).

2.6 Ring-closing metathesis of PEB

Ring-closing metathesis of simple diene-ethers to generate an unsaturated oxygen heterocycle has been extensively explored.[47-48] High yields were typically observed in reactions involving the formation of five- and six-membered rings. Here, RCM will be applied on PEB aiming to produce functionalisable cyclopolyether (FCPE) made of six-membered unsaturated ring monomer units. Although RCM on (*a*)-PEB will not give a stereocontrolled cyclopolyether (Scheme 2.7 - A), it was used to establish optimum cyclisation conditions. For this purpose, a low molecular weight of (*a*)-PEB ($M_{n,GPC}$ = 2100) was treated with ruthenium carbene catalysts such as 1st generation Grubbs catalyst **(1.28)** and 2nd generation Hoveyda-Grubbs catalyst **(1.30)** (Scheme 2.9). The reactions were conducted under static vacuum (evacuating the filled gas (N_2 or Ar) in the ampoule by vacuum then sealing the reaction ampoule) using dichloromethane (DCM) as a solvent at different concentrations (based on the monomer molecular weight). As expected, the rate of reaction of terminal alkenes to internal alkenes increased by increasing the concentration of the reactants (Table 2.2). Also, when **(1.30)** catalyst used, the conversions were significantly higher at all

concentrations compared to **(1.28)**. This can be accounted for by the higher reactivity of **(1.30)** and the poor thermal stability of **(1.28)**.[49-50]



Scheme 2.9 RCM of (*a*)-PEB using 1st generation Grubbs catalyst (**1.28**) and 2nd generation Hoveyda-Grubbs catalyst (**1.30**).

However, the molecular weights of the produced polymer were not calculated in GPC, due to overlap with eluent peaks. For this reason, higher molecular weight starting polymers of PEB were required.

Table 2.2: RCM of (*a*)-PEB using 1st generation Grubbs catalyst **(1.28)** and 2nd generation Hoveyda-Grubbs catalyst **(1.30)**.

[Olefin][a] M	Con.(%)[b] (1.28)	Con.(%)[b] (1.30)
0.05	43	80
0.1	61	90
0.15	68	93

[a] PEB $M_{n,GPC}$ 2100 and Đ 1.19 in DCM under reflux with [Olefin]:[Catalyst] = 20:1; Time 43 hours; [b] Determined by ^{1}H-NMR spectroscopy of olefin peaks integration of the produced polymer.

Here, the higher molecular weight sample ($M_{n,GPC}$ = 3200) was treated with 2nd generation Hoveyda-Grubbs catalyst (**1.30**) at a higher temperature using 1,2-dichloroethane (DCE) as a solvent at two different higher concentrations. The reaction was quenched after 72 h and showed completion for both concentrations. The GPC data showed an apparent molecular weight loss on ring-closing, correlating well with the loss of a single ethylene molecule per repeat unit. When concentrations were kept at 0.2 M (Table 2.3, entry 1), no cross-linking was observed, and polymer dispersity and viscosity remained similar. However, at higher concentrations (0.4 M),

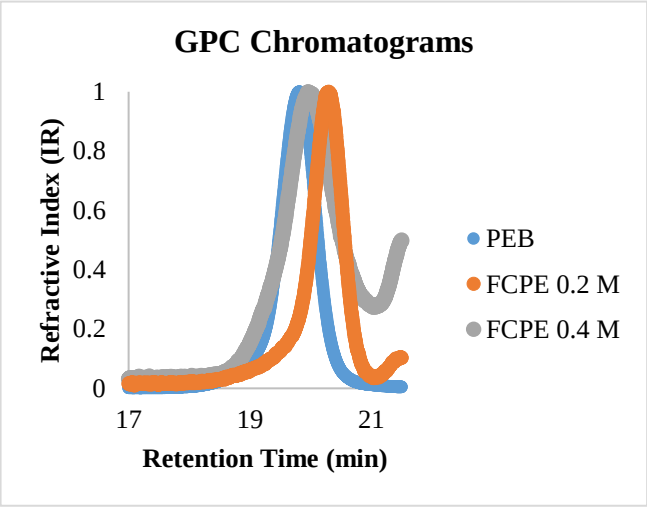
competition between ring-closing and polymer cross-linking occurs, as evidenced by the formation of a high molecular shoulder in GPC traces (Figure 2.7).[16]

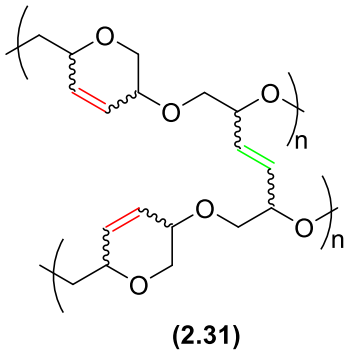
Table 2.3: RCM of (*a*)-PEB using 2nd generation Hoveyda-Grubbs catalyst **(1.30)**.

Entry[a]	[Olefin]	$M_{n,st}$[b]	$Đ_{st}$[b]	Con. (%)[c]	$M_{n,th}$[d]	M_n[b]	$Đ$[b]
1	0.2	3200	1.19	99	2540	2500	1.21
2	0.4	3200	1.19	99	2540	2900	1.32

[a] Reactions performed in DCE at reflux with 5 mol% of **1.30** for 72 h. [b] M_n and Đ determined by GPC *vs* uncorrected PS standards. [c] Determined by ^{1}H-NMR spectroscopy by integrating the olefin peaks in the resultant polymer. [d] $M_{n,th}$ = PEB $M_{n,GPC}$ × 0.8 due to the expected loss of one C_2H_4 per monomer unit.

It was not possible to distinguish between the cyclised alkenes and the crossed alkenes in NMR spectroscopy due to the broadness of the peaks. ^{1}H-NMR spectra showed only the conversion of terminal alkenes of PEB into internal alkenes (Figure 2.8). The conversion of the RCM reaction was determined by ^{1}H-NMR spectroscopy by calculating from the relative integrations values of the olefin peak attributed to the polymer. In the starting polymer, the ratio of the internal olefin proton (δ = 5.77-5.69) to the two terminal protons (δ = 5.33-5.13) is 100 to 200. Hence, in the resulting polymer the integral of the peak of resulting internal olefin protons (δ = 6.32-5.71) we normalised to 100, then we measured how many terminal olefin protons left (not reacted). If the integration was 100 to 20 this means that the 100 internal olefin protons contain 10 internal olefin protons from the starting polymer. Hence, the conversion of reaction is 90 %.





(2.31)

Figure 2.7: Gel Permeation Chromatography (GPC) chromatograms of PEB and FCPE at 0.2 and 0.4 M concentrations (left). Possible structure (**2.31**) of partially crossed FCPE at 0.4 M concentration.

Also, the internal olefins in ^{13}C-NMR spectra of the atactic cyclopolyether produced were broad and multiple, as expected due to the different conformations of atactic FCPE (*a*-FCPE, Figure 2.9 and Scheme 2.7 - A).

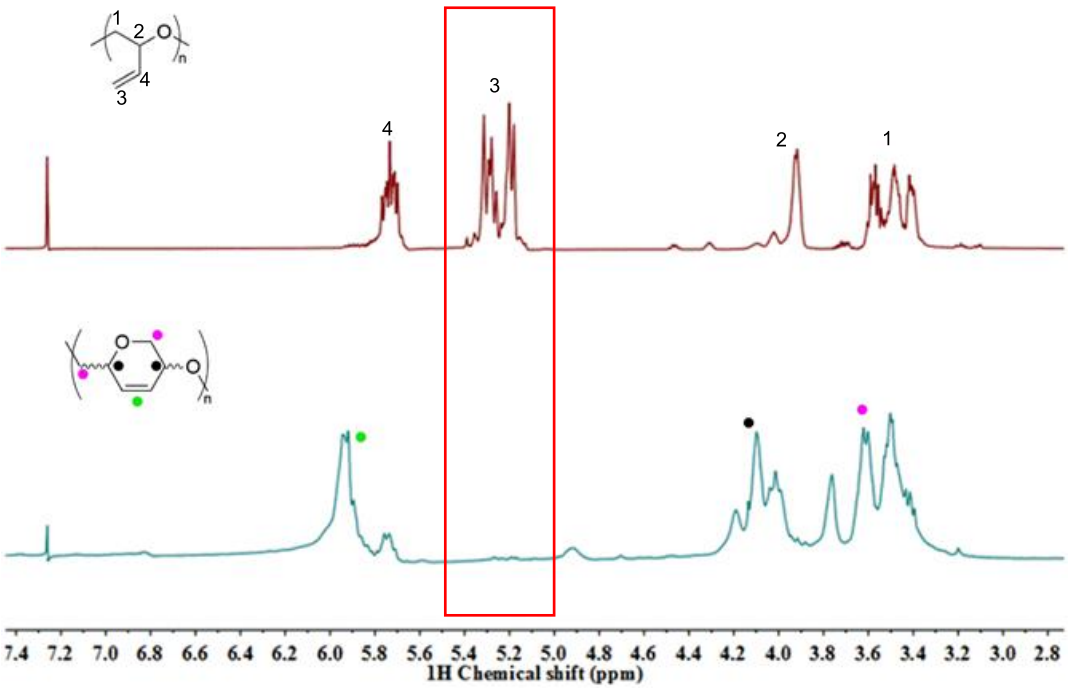


Figure 2.8 ^{1}H-NMR (*CDCl*$_3$, 500.2 MHz) of (*a*)-PEB (top) and (*a*)-FCPE (bottom).

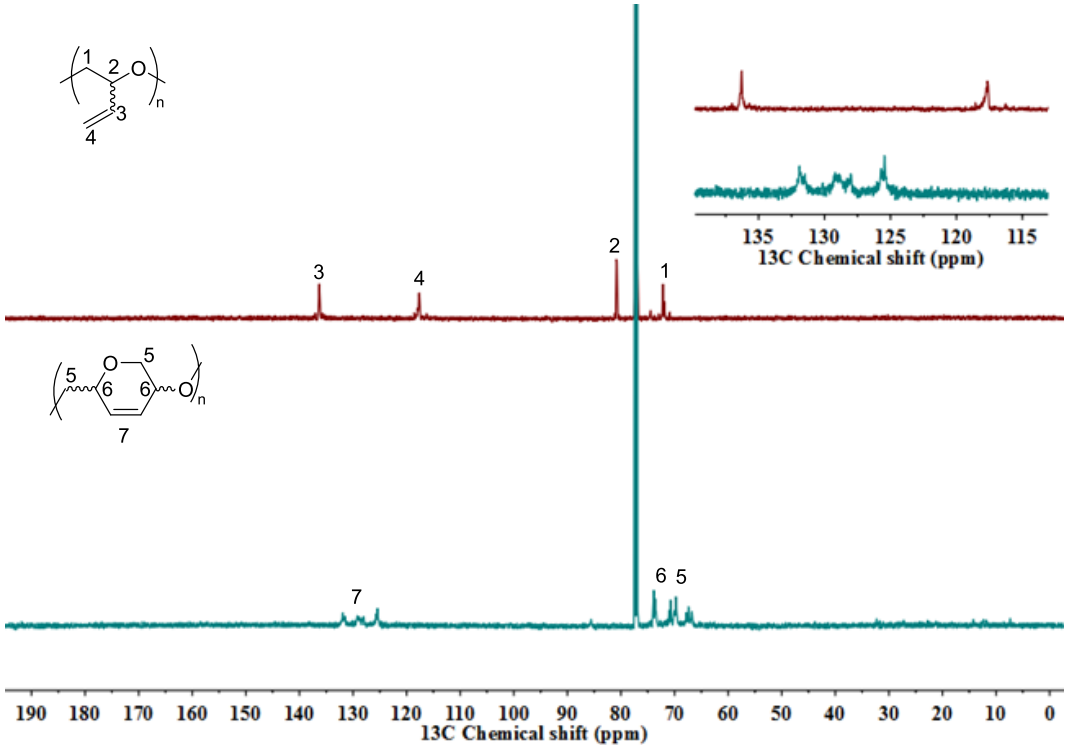


Figure 2.9 ^{13}C-NMR (*CDCl*$_3$, 125.8 MHz) of (*a*)-PEB (top) and (*a*)-FCPE (bottom).

However, the RCM reaction was further optimised before working with the isotactic structure. To demonstrate the solvent and temperature effect, the reaction was studied at different temperatures using solvents that easily dissolve PEB and are compatible with the used metathesis catalyst.[51] Although the (*a*)-FCPE produced was soluble in a wide range of solvents from diethyl ether to methanol, the commonly used solvents in metathesis reactions are DCM, chloroform, tetrahydrofuran (THF) and DCE. The results obtained when using these four solvents demonstrated that the reaction is fast to show ≥90% conversion after 30 min only in all reactions. The high boiling point solvent (DCE) showed the fastest conversion rate compared to DCM, THF and chloroform (Table 2.4). This result is also supported when the isotactic PEB used (Table 2.7). Moreover, running the reaction at two different catalyst ratios (5 mol % and 2 mol %) illustrated that the reaction rate is highly dependent on the catalyst loading (Table 2.5). Higher catalyst load led to a higher conversion rate.

Table 2.4: RCM of (*a*)-PEB in different solvents at different temperatures.[a]

Solvent	Temp. (°C)	Con. (%)[b]
DCM	40	92
$CHCl_3$	62	90
THF	62	92
DCE	84	94

[a] [PEB] = 0.2 M, $M_{n,GPC}$ 3200 and Đ 1.19; Time 30 min; [Olefin]:[**1.30**] = 20:1; [b] Determined by ^{1}H-NMR spectroscopy of olefin peaks integration of the produced polymer.

Table 2.5: RCM of atactic PEB at two different catalyst ratio of **1.30** catalyst.[a]

Time (h)	Con. (%)[b] using two catalysts ratios	
	(5 mol %)	(2 mol %)
T_1 (0.5)	94	92
T_2 (22)	97	95
T_3 (43)	98.5	96
T_4 (72)	>99	96

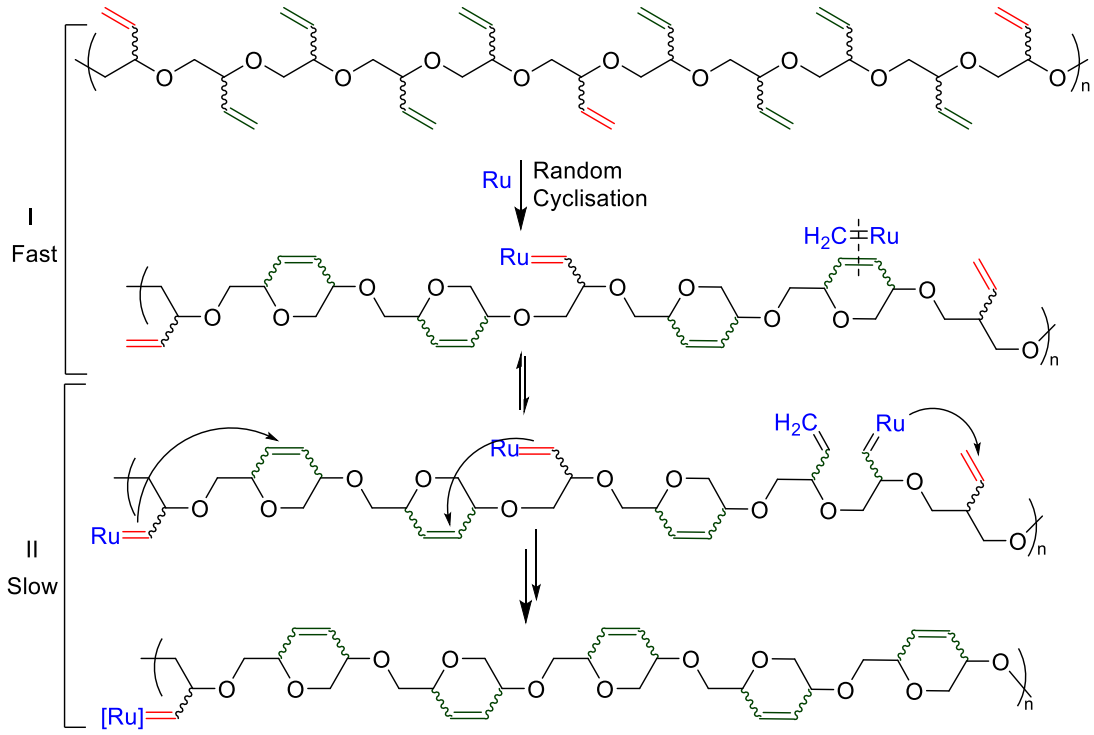
[a][PEB] = 0.2 M, $M_{n,GPC}$ 3200 and Đ 1.19 in DCE under reflux; [b] Determined by ^{1}H-NMR spectroscopy of olefin peaks integration of the produced polymer.

This kinetic profile of Table 2.5 suggests a mechanism originally proposed by Coates and Grubbs (Scheme 2.10):[37]

(i) A fast stage; when the catalyst attacks and cycles the olefins of the polymer randomly but only isolated olefins remain, and

(ii) A slow stage when the rings rearrange along the chain until all olefins are cyclised. This requires that the cyclised olefins can undergo further metathetic reactions, enabling a re-opening and exchange of the product rings.

This suggests that the allyl ether of PEB is type I alkene that can undergo fast homodimerisation, and the formed cycles readily able to react in a secondary metathesis reaction with the adjacent non-cycled allyl ether.[52]



Scheme 2.10 Proposed kinetic mechanism of RCM of poly(epoxybutene).

The RCM kinetic profile was studied in two reactions; one under static vacuum and one under 1 atm. of ethylene gas. In the first 30 minutes, both reactions were carried out under static vacuum and showed 95 % conversion for (*a*)-PEB (M_n = 2100, Đ 1.16) to (*a*)-FCPE. After that, one of the reaction ampoules was placed under ethylene gas, while the other continued under static vacuum. The kinetic profile showed that while the reaction continued to completion under static vacuum, the one under ethylene

slowed down to yield only 97% conversion (Figure 2.10). It seems that under ethylene environment the reaction is in a state of equilibrium with methylidene ruthenium complex and ethylene gas (a so-called nonproductive process). This would open some cycles and then decompose the catalyst (Scheme 2.11).[53]

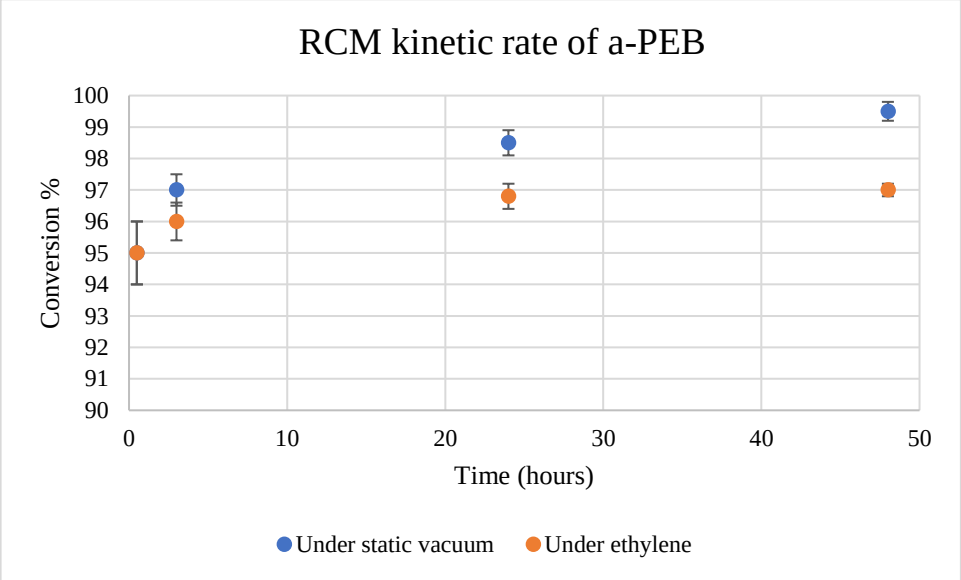
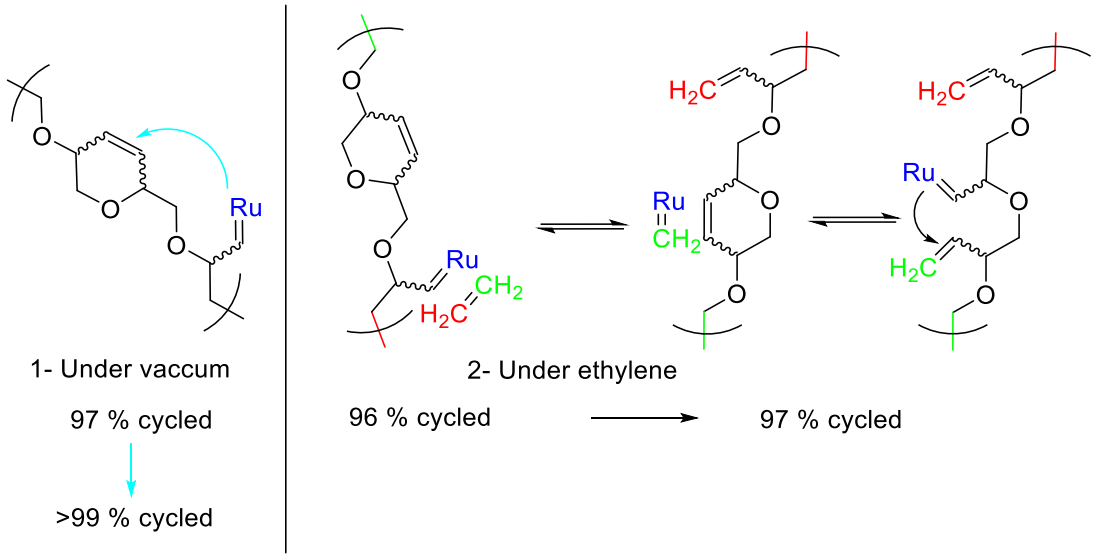


Figure 2.10 The RCM of atactic PEB, $M_{n,GPC}$ 2100 and Đ 1.16, kinetic profile at [PEB] = 0.2 M using 5% of **1.30** catalyst in DCE under reflux monitored by ^{1}H-NMR spectroscopy (N=3).



Scheme 2.11 Possible kinetic mechanism of RCM of (*a*)-PEB under static vacuum (left) and under ethylene gas (right).

Optimal ring-closing conditions for PEB included the use of 5 mol% of the 2nd-generation Hoveyda-Grubbs **(1.30)** catalyst, at high concentrations of polymer (0.2 M respective to monomer unit) under static vacuum in refluxing DCE. The reaction was carried out using different molecular weights of PEB and it was observed that the

reaction rate is dependent on the molecular weights of the starting polymer. Higher molecular weight took a significantly longer time for completion (Table 2.6).

Table 2.6: RCM of different molecular weights of atactic PEB.[a]

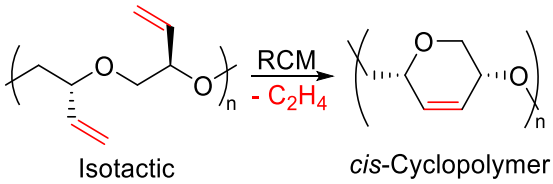
(a)-PEB M_n[b]	$Đ$ [b]	Time (days)	Con.(%)[c]	*(a)*-FCPE $M_{n,th}$[d]	*(a)*-FCPE M_n[b]	$Đ$ [b]
3200	1.19	3	>99	2500	2500	1.21
4400	1.18	5	>99	3500	2700	1.22
5400	1.17	7	>99	4300	3100	1.22
6550	1.19	8	>99	5230	3700	1.26

[a] The reaction was carried out in DCE under reflux and [PEB] = 0.2 M; [Olefin]:[**1.28**] = 20:1; [b] M_n and Đ determined by GPC *vs* uncorrected PS standard; [c] Determined by monitoring the reaction daily by ^{1}H-NMR spectroscopy; [d] (*a*)-FCPE $M_{n,}$ theoretical = (*a*)-PEB $M_{n,GPC}$ × 0.8 (due to 20% mass loss of ethylene per cyclomonomer unit) + [$M_w(CH_2)$ × unreacted olefin %].

The optimised RCM conditions could be then applied to the isotactic poly(epoxy-butene) (*i*-PEB) to afford a stereocontrolled FCPE.

2.7 RCM: (*a*)-PEB *vs* (*i*)-PEB

This new polymer (*a*-FCPE) represents the first synthetic cyclo-polyether prepared, yet its inherent atacticity prevents any overall conformational control. Thus, isotactic-rich PEB [(*R*)-PEB] (**2.29**) was synthesised by ROP of the (*R)* enantiomer of EB (95:5 er), which was prepared from racemic EB using Jacobsen's hydrolytic kinetic resolution. The behaviour of the isotactic polymer towards RCM was directly compared to that of its atactic derivative under the previously optimised conditions (Figure 2.11).



(2.29) **(2.32)**

Scheme 2.12 RCM of *(R)*-PEB (**2.29**) to *(R)*-FCPE (**2.32**).

The rates of cyclisation of the enantiomerically rich monomer were significantly slower than for the racemic monomer. Plotting reaction kinetics (Figure 2.11) showed that the cyclisation reaction progressed quickly in the beginning, with 94% of the

pendant vinyl groups disappearing within 30 min for both atactic and isotactic derivatives determined by ^{1}H-NMR spectroscopy as detailed earlier on page 43. The metathesis reaction then significantly slowed down, especially for the more conformationally rigid isotactic derivative.

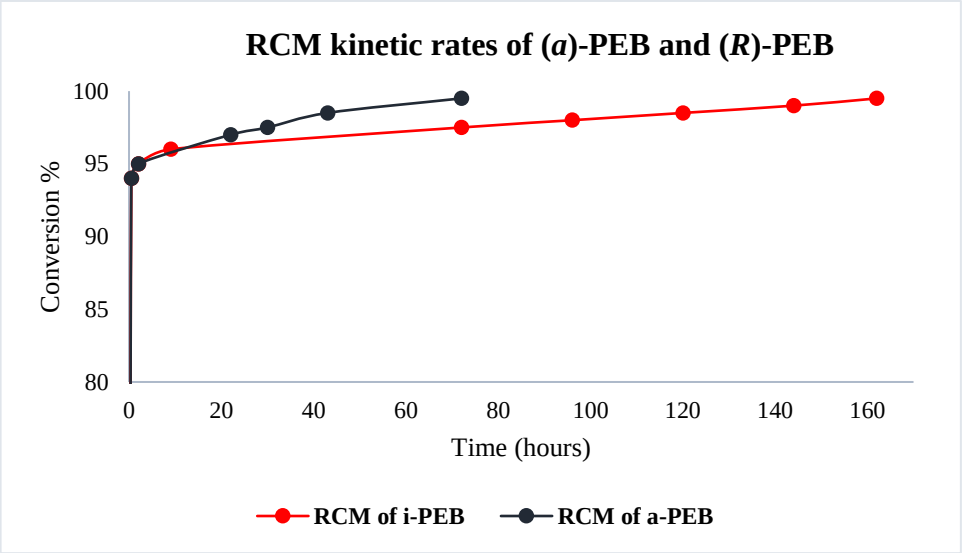


Figure 2.11 The RCM of (*a*)-PEB, $M_{n,GPC}$ 3200 and Đ 1.19 and (*R*)-PEB, $M_{n,GPC}$ 3940 and Đ 1.15 kinetic profile at 0.2 M using 5% of **1.30** catalyst in DCE under reflux monitored by ^{1}H-NMR spectroscopy (N=1).

Moreover, the RCM rate of the isotactic version was significantly slower than the atactic one at relatively low temperature. Carrying out the reaction in DCM did not show completion even after 14 days (Table 2.7).

Table 2.7: RCM of (*a*)-PEB and (*R*)-PEB at two different temperatures.[a]

Polymer	Solvent	Temp. (°C)	Time (days)	Con.[b] (%)
Atactic	DCM	40	5	98
Isotactic	DCM	40	7	95
Isotactic	DCM	40	14	97
Atactic	DCE	84	5	99
Isotactic	DCE	84	7	99

[a][PEB] = 0.2 M; (*a*)-PEB-$M_{n,GPC}$ 4400 and Đ 1.18; (*R*)-PEB-$M_{n,GPC}$ 3940 and Đ 1.15; [Olefin]:[**1.30**] = 20:1; [b] Determined by ^{1}H-NMR spectroscopy of olefin peaks integration of the produced polymer.

Fixing the free rotation of the pendent olefins through RCM impacts the glass transition temperature (T_g) in both (*a*)- and (*i*)-PEB. The organised structure of *(R)*-FCPE has a significantly higher T_g *vs* (*a*)-FCPE (-10.6 °C *vs* -26.7 °C) (Table 2.8). This is consistent with the presence of cycles hindering segmental chain mobility in both structures.

Table 2.8: RCM of PEB with catalyst **1.30**.

Entry[a]	PEB M_n[b]	$Đ$[b]	T_g °C[c]	Time (days)	FCPE		$Đ$[b]	T_g °C[c]
					$M_{n,th}$[d]	M_n[b]		
Atac.	4400	1.18	-56.5	5	3500	2700	1.22	-26.7
Iso.	3940	1.15	-53.8	7	3150	2600	1.19	-10.6

[a][PEB] = 0.2 M; the reaction conversion was monitored daily until >99% by ^{1}H-NMR spectroscopy using 1,2-DCE at reflux with 5 mol% 2nd H-G catalyst. [b] M_n and Đ determined by GPC *vs* uncorrected PS standards. [c] Determined by differential scanning calorimetry. [d] $M_{n,th}$ = PEB $M_{n,GPC}$ × 0.8.

A better understanding of the mechanism can be drawn from the ^{13}C-NMR spectra of both atactic and isotactic FCPE and PEB (Figure 2.12), which demonstrate that greater than 99% of the olefins of PEB are cyclised (Figure 2.12, B and E). In the atactic FCPE (Figure 2.12, B), the new olefin peaks appear as broad, overlapping resonances (δ 125-132), reflecting the different ring configurations along the polymer backbone. On the other hand, the isotactic derivative *(R)*-FCPE showed only two sharp olefin resonances (Figure 2.12, E), confirming the stereocontrolled structure of the polymer (*cis*-cyclopolymer). However, the ^{13}C-NMR spectrum (Figure 2.12, D) of *(R)*-FCPE after 94% conversion (determined by ^{1}H-NMR spectroscopy), which was taken after 30 min, showed the uncyclised isolated olefin peaks (δ 118.3 and 135.6) and several cyclic olefin peaks (δ 125-132). At the end of the reaction, the two peaks of the uncyclised isolated olefin and most of these cyclic olefin peaks were not observedn (after 7 days) (Figure 2.12, E), which purports that in the initial metathesis stage when the catalyst randomly forms different ring sizes (Scheme 2.13). In the subsequent slow stage, rings rearrange along the chain until only the most thermodynamically stable 6-membered rings are present. The resulting cyclic monomer unit of *(R)*-FCPE exists as *cis* stereoisomers with two olefin peaks corresponds to pseudoaxial and pseudoequatorial of the ring's substituents. Not only ^{13}C-NMR showed two singlet

olefin peaks of *(R)*-FCPE, the olefin protons peak was narrower than in it was in *(a)*-FCPE (Figure 2.13 *vs* Figure 2.8). In addition, the ^{1}H-Dept 135 HSQC NMR spectrum of the fully cyclised *(R)*-FCPE showed the expected six singlet carbon peaks of the six-membered ring unit matching the proton peaks (Figure 2.13).

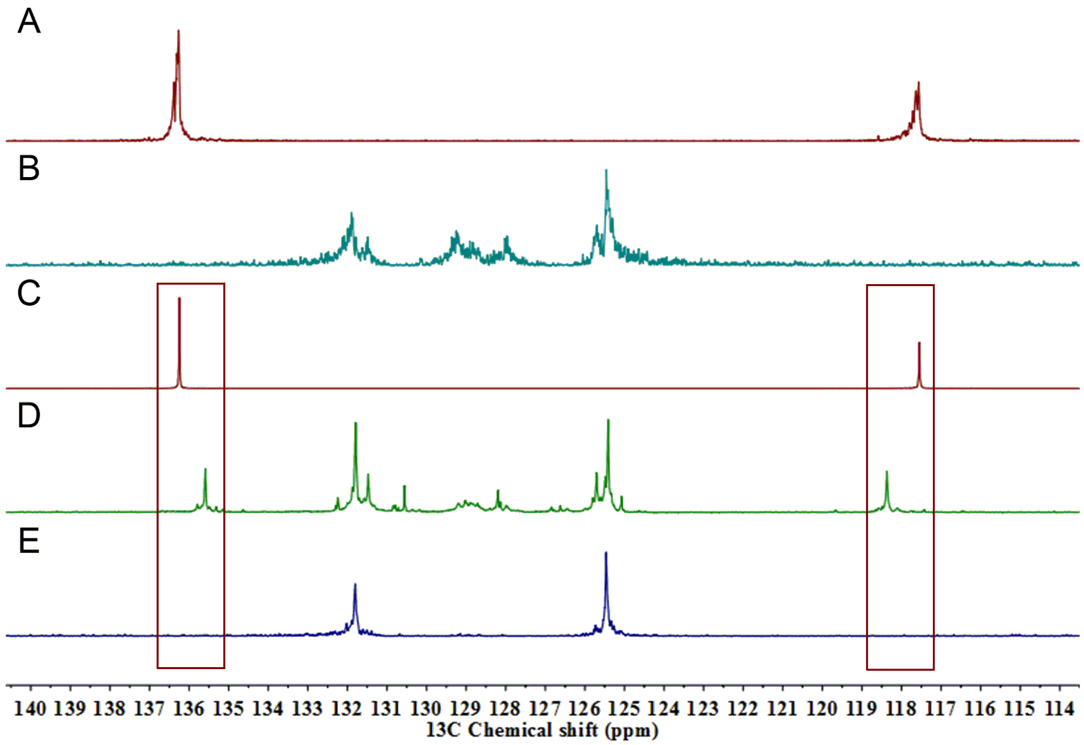
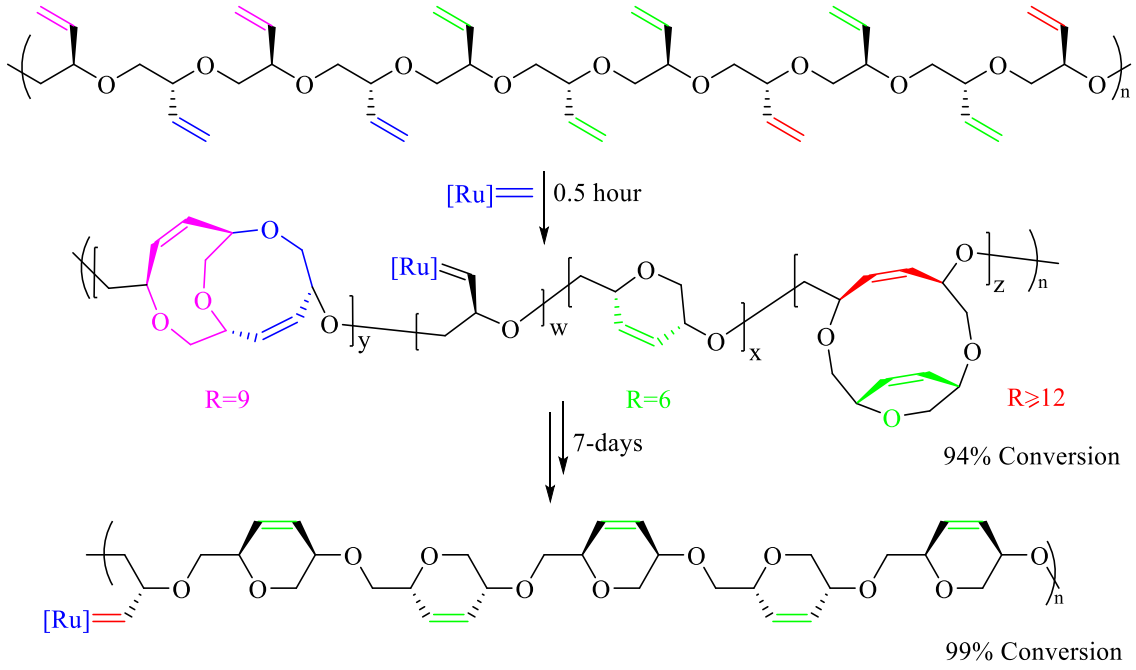


Figure 2.12 ^{13}C-NMR of olefin region in $CDCl_3$ of: (A) *(a)*-PEB, (B) *(a)*-FCPE, (C) *(R)*-PEB, (D) metathesis product of *(R)*-PEB after 30 min (94% conversion) and (E) metathesis product of *(R)*-PEB after 7 days (>99% conversion determined by ^{1}H-NMR spectroscopy).



Scheme 2.13 Proposed kinetic mechanism of RCM of *(R)*-PEB.

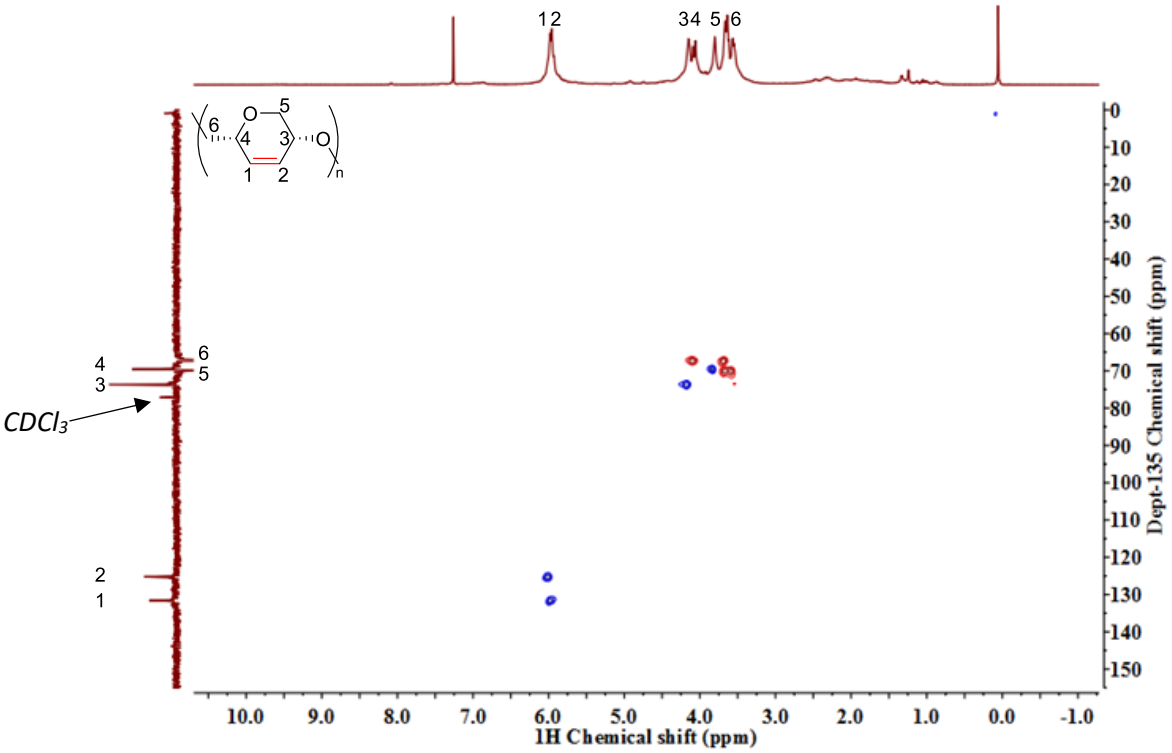


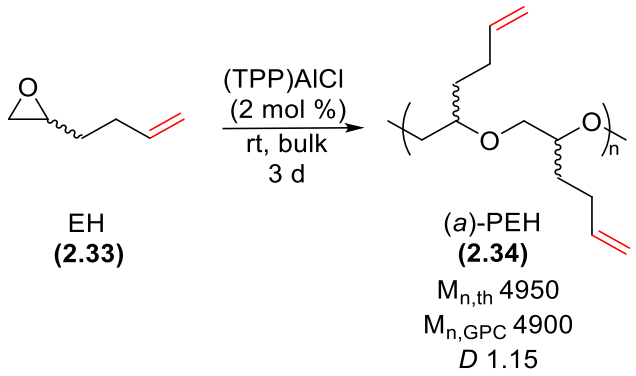
Figure 2.13 ^{1}H-Dept 135 HSQC (*CDCl*$_3$, 500.2 MHz) of isotactic functionalizable cyclopolyether; *(R)*-FCPE (**2.32**).

An isotactic functionalisable cyclopolyether has been obtained and the resulting olefin group can be further functionalised.

2.8 Large-rings cyclopolyethers

Polyethers chains in solvents may have an unlimited number of conformations due to their backbone flexibility. This would explain why the initial metathesis stage of PEB could form different ring sizes as initial kinetic cycles. However, the RCM reaction is reversible and under thermodynamic control. Therefore, these kinetic rings would open and the resulting uncycled pendent olefins would reenter the metathesis reaction with the adjacent olefin to make the most thermodynalmically stable 6-membered rings. This behaviour raised the question of whether RCM can be used to make a cyclopolyether made of medium-rings size, ≥10-membered-ring. To demonstrate this, we performed a RCM reaction on atactic poly(epoxyhexene) (*a*-PEH) (Scheme 2.14). (*a*)-PEH (**2.34**) was prepared by ROP of a commercially available racemic monomer, 1,2-epoxy-5-hexene (EH, **2.33**), following the conditions that were used for (*a*)-PEB synthesis. The ROP of EH by (TPP)AlCl was controlled to afford the desired starting

polymer structure, confirmed by proton NMR spectroscopy (Figure 2.14), with the desired molecular weight and a narrow dispersity confirmed by GPC.



Scheme 2.14 Ring-opening polymerisation of 1,2-epoxy-5-hexene by (TPP)AlCl initiator.

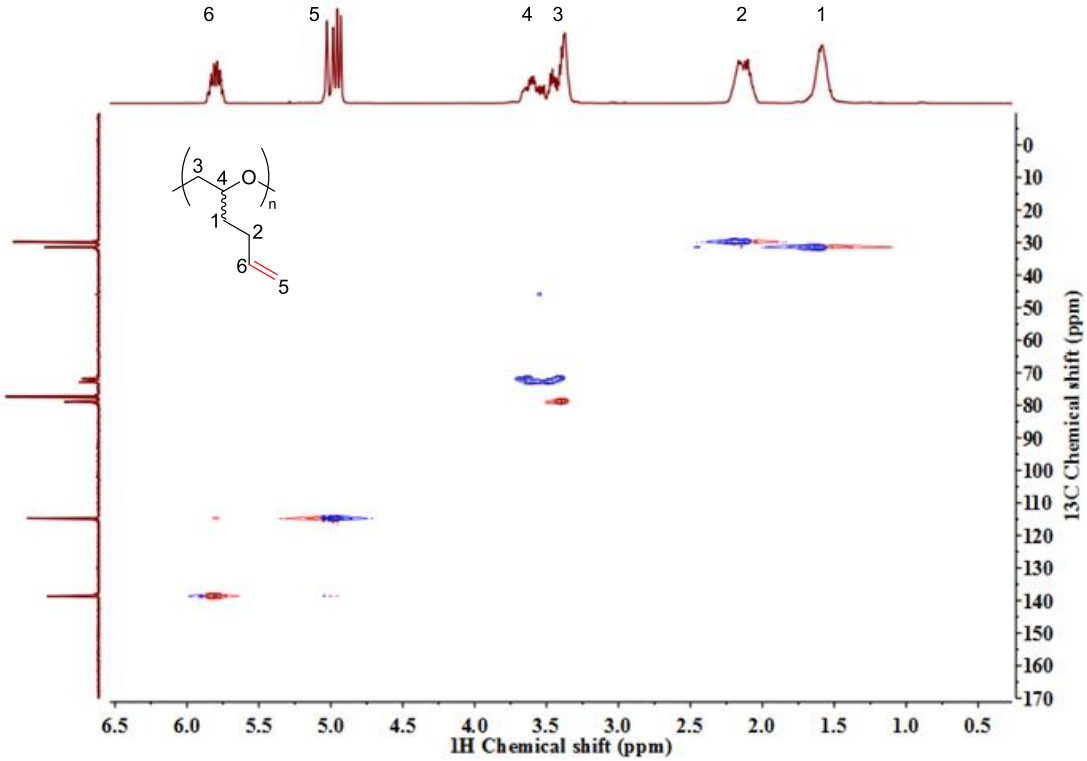


Figure 2.14 ^{1}H-^{13}C HSQC ($CDCl_3$, 500.2 MHz) of atactic poly(epoxyhexene) (*a*-PEH).

Then, (*a*)-PEH was treated with the same RCM reaction conditions that were used before with PEB using DCM as a solvent. (*a*)-PEB, with a similar molecular weight (M_n), was also used as a reference to compare the behaviours of these two polymers under these RCM reaction conditions (Table 2.9). Firstly, the reaction was conducted for 30 min with a starting polymer concentration of 0.2 M [olefin – based on monomer molecular weight] (Table 2.9 - entries 1 and 2). The conversion of the terminal olefins to internal olefins was around 90% in both polymers. Also, as expected, the (*a*)-PEB

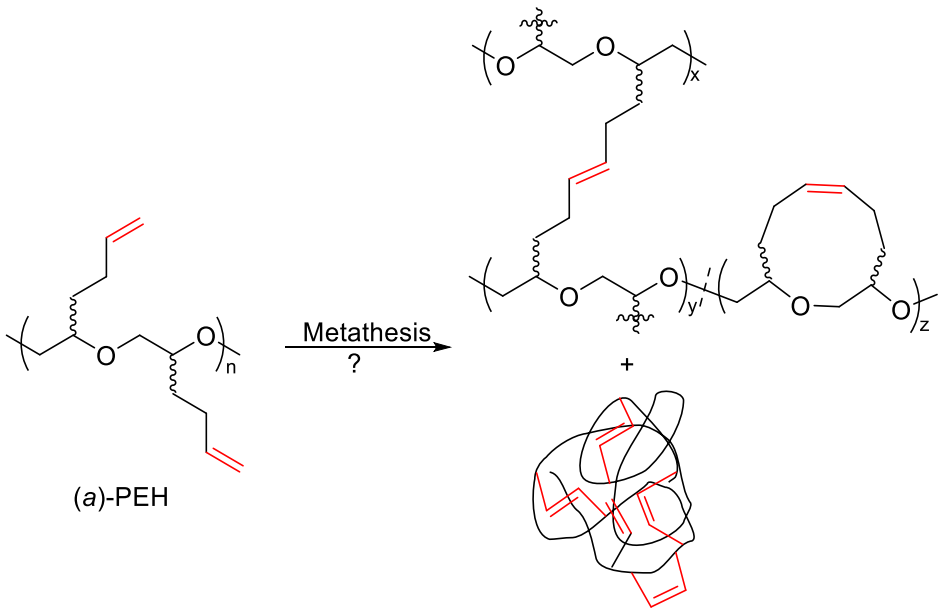
tended to form rings rapidly, as exhibited by a decrease in the apparent M_n with similar dispersity *Đ*. However, (*a*)-PEH showed a different behaviour from (*a*)-PEB; it demonstrated mainly cross-linking metathesis (intermolecular), as exhibited by an increase in the apparent molecular weight (M_n) and a broadening of the molecular weight distribution *Đ* (from 1.15 to ~ 3).

Table 2.9: Comparison between PEB and PEH behaviours in metathesis reaction.[a]

Entry	Polymer	M_n [b]	*Đ* [b]	[Olefin] M	Time (h)	Con.[c] (%)	$M_{n,th}$[d]	M_n [b]	*Đ* [b]
1	PEB	4380	1.18	0.2	0.5	92	3610	2750	1.22
2	PEH	4880	1.15	0.2	0.5	88	4340	14700	2.95
3	PEB	4380	1.18	0.015	12	90	3650	3700	1.21
4	PEH	4880	1.15	0.015	12	94	4270	14625	3.31

[a] The reaction was carried out in DCM under reflux; [Olefin]:[**1.30**] = 20:1; [b] M_n and *Đ* determined by GPC *vs* uncorrected PS standard; [c] Determined by ^{1}H-NMR spectroscopy; [d] M_n theoretical = $M_{n,GPC} \times 0.8$ or 0.834 (due to 20% or 16.67% mass loss of ethylene per cyclomonomer unit of PEB and PEH, respectively) + [$M_w(CH_2) \times$ unreacted olefin %].

To minimise this intermolecular metathesis between the (*a*)-PEH chains, the reaction was repeated at a lower concentration (0.015 *vs* 0.2 M) and for longer time (12 *vs* 0.5 h) (Table 2.9 - entries 3 and 4).



Scheme 3.15 Possible intramolecular and intermolecular metathesis products of (*a*)-PEH.

However, similar results were obtained, showing RCM of a polymer with longer pendent olefins to form medium (8–11 membered rings) is more difficult. The medium

rings not only have a kinetic disadvantage, but also suffer from unfavourable transannular interactions.

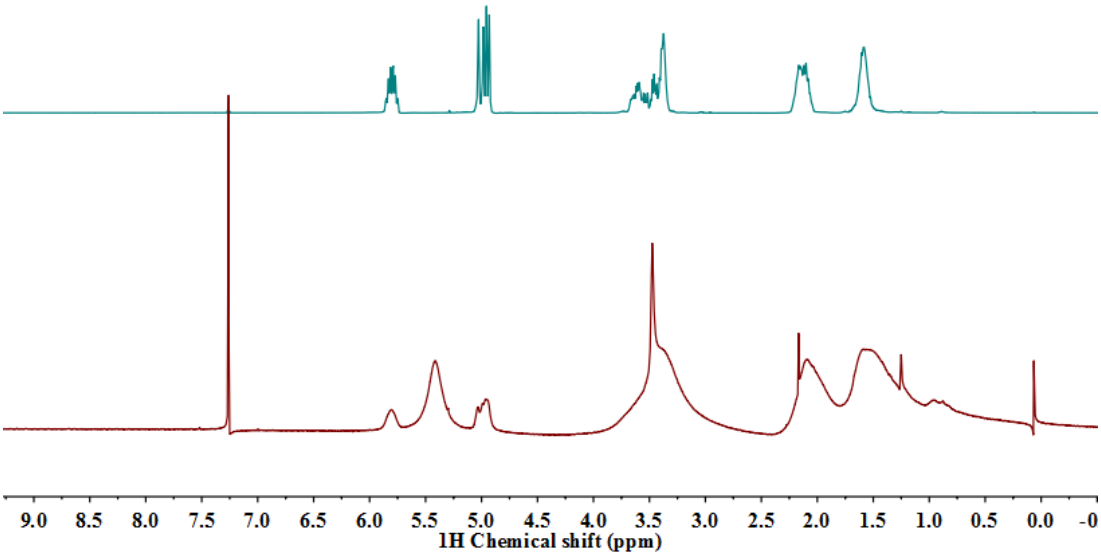


Figure 2.15 ^{1}H-NMR (*CDCl*$_3$, 500.2 MHz) of atactic PEH (top) and the metathesis product of PEH (88% con.) (bottom).

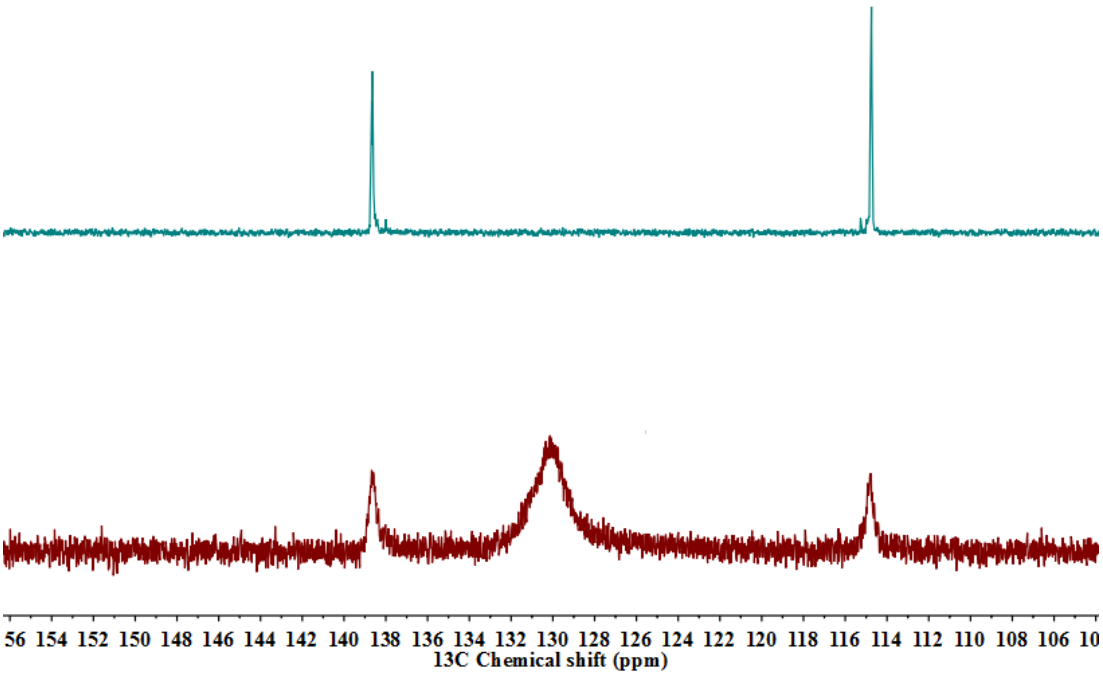


Figure 2.16 ^{13}C-NMR (*CDCl*$_3$, 125.8 MHz) of the olefin region of atactic PEH (top) and the metathesis product of PEH (88% con.) (bottom).

The broad peaks in the NMR spectra (Figures 2.15 and 2.16) of the metathesis product of (*a*)-PEH were not conclusive whether the product is exclusively cross-linked polymers or a mixture of intramolecular and intermolecular metathesis products (Scheme 2.15). These results supported the hypothesis that preparing cyclopolymers by RCM is only possible for the small ring size (five to seven).

2.9 FCPE functionalisation

The cyclic monomer unit of the produced functionalisable cyclopolyether (FCPE) contains an alkene, and this makes FCPE an excellent platform for a wide range of functionalisation reactions. The stereoselectivity of the functionalisation reactions would probably depend on the functionalising agent used and the steric hindrance of the rings' substituents. Thus, for structural control, it is imperative to work with (*i*)-FCPE, where the 1,4-links would be indiscriminately *cis*. While the alkene group can be transformed into many functional groups, hydroxyl groups were our main interest. The introduction of hydroxyl groups into the polyether backbone is important since alcohols show versatile reactivity and are essential for biomedical applications as they are non-toxic.[54] Introducing two vicinal hydroxyl groups from an alkene can be achieved either by dihydroxylation or by hydrolysing the epoxide derivative of the alkene.

2.9.1 Dihydroxylation

Dihydroxylation of the alkene group of the *cis*-cyclopolymer will occur exclusively from the top face, which is not hindered by the two substituents. This would afford a novel polymer family encompassing a poly(ethylene glycol) backbone and sugar-like functionalities so-called "PEGose". PEGose structure mimics amylose (**2.35**) with the glycosidic bond of amylose replaced by a non-hydrolysable ether link (Figure 2.17). To prepare the PEGose polymer, hydrogen peroxide and potassium permanganate oxidation conditions were initially used but did not yield the desired structure.[55] *(R)*-FCPE, however, was successfully dihydroxylated under mild conditions using *N*-methylmorpholine *N*-oxide (NMO) and osmium tetroxide (OsO_4) as a catalyst (Scheme 2.16).[56]

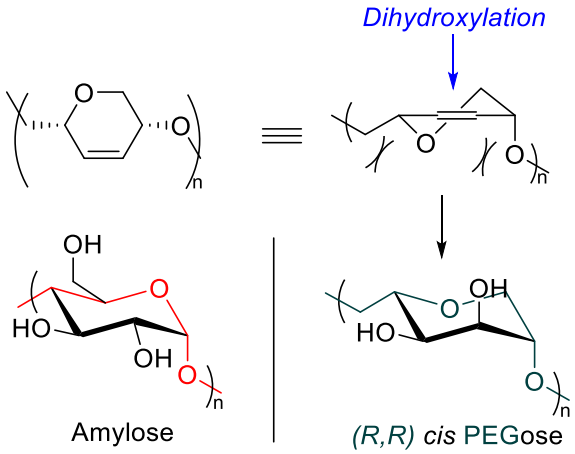
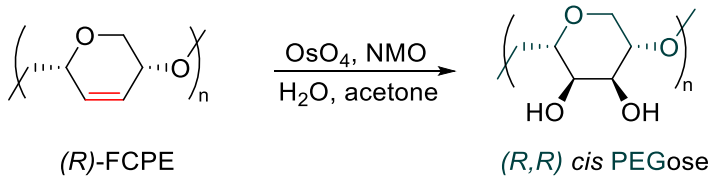


Figure 2.17 Diastereoselectivity of *(R)*-FCPE dihydroxylation leads to *(R,R) cis* PEGose which mimics amylose.



Scheme 2.16 Diastereoselective dihydroxylation of *(R)*-FCPE by OsO_4 to *(R,R) cis* PEGose.

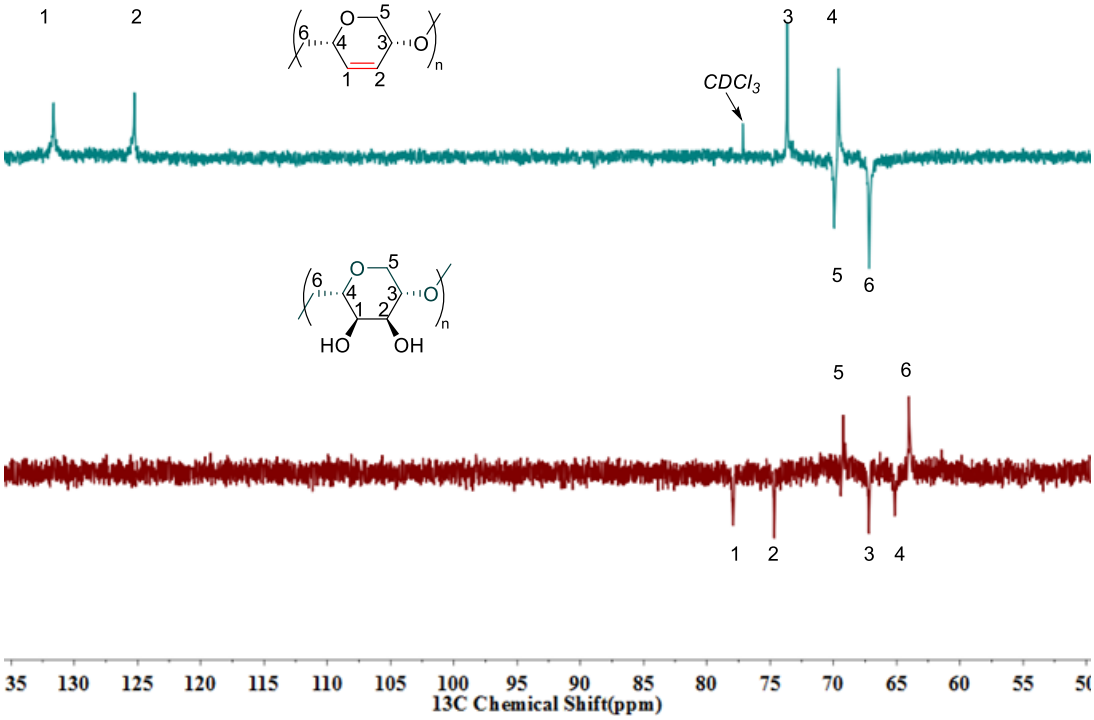
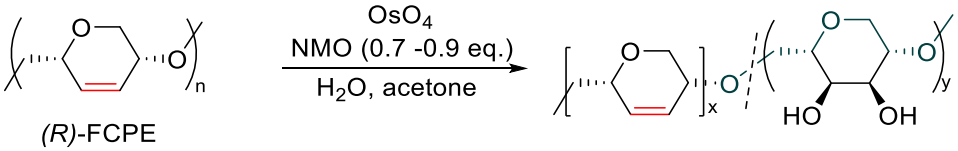


Figure 2.18 Dept 135 NMR spectroscopy (100 MHz) of *(R)*-FCPE (**2.32**) in $CDCl_3$ (top) and *(R,R) cis* PEGose (**2.36**) in D_2O (bottom).

This second post-polymerisation functionalisation was diastereoselective, as OsO_4 attacks on the less hindered side of the ring, as demonstrated by NMR spectroscopy (Figure 2.18), where only two new carbons of the two hydroxyls appeared in the ^{13}C-NMR spectrum. This dihydroxylation produces a unique stereocontrolled polymer structure, with a hydrophilic surface (*cis*-diols) opposite the hydrophobic backbone. The solubility of starting and resulting polymers was tested visually by adding 10 mL of selected solvents to around 50 mg of the polymer. The parent polymer (*i*-FCPE) showed a good solubility in a wide range of organic solvents from diethyl ether (DEE) to methanol (MeOH), while the fully dihydroxylated polymer (PEGose) was freely soluble in polar solvents only such as, water and dimethyl sulfoxide (DMSO) (Entry A and D, respectively in Table 2.10). However, this functionalisation strategy allows for a broad range of polymer polarities to be accessed. Since excess NMO affords complete dihydroxylation of the double bonds, the reaction also offers the ability to adjust the polymer polarity by limiting the amount of co-oxidizing reagents, thereby offering a secondary tuning for biomedical applications and leaving sites remaining for further functionalisation or drug conjugation (Scheme 2.17).



(R)-FCPE

(2.32)

(2.37)

x + y = n

Scheme 2.17 Partial dihydroxylation to afford a copolymer of (*R*)-FCPE-co-(*R,R*) *cis* PEGose.

Reducing the NMO loading from 1.1 to 0.7 equivalents limits the dihydroxylation ratio to give a copolymer of (*R*)-FCPE and PEGose. Consequently, varying the ratio of (*i*)-FCPE to PEGose alters the polarity and solubility of the resultant polymers (Scheme 2.17, Table 2.10 and Figure 2.19). Full olefin conversion was observed, as demonstrated by ^{1}H-NMR spectroscopy (D, Table 2.10 and Figure 2.19). However, reducing the NMO loading from 1.1 to 0.9 equivalents yielded 91% conversion of the olefins to diols confirmed by reducing the olefin protons ratio of the parent polymer

(*i*)-FCPE from 25% to 2.25% in the resulting partially dihydroxylated polymer (C, Table 2.10 and Figure 2.19).

The conversion was determined using the ^{1}H-NMR spectroscopy. Both monomer units in **2.37** polymer contain 8 protons (excluding the -OH protons). In the non-dihydroxylated unit, the percentage of the two protons of the olefin to the total protons in the unit is 25% (Figure 2.19 - A, Table 2.10 - Entry A). While in the dihydroxylated unit (Figure 2.19 - D, Table 2.10 - Entry D), the 8 protons are all in 3.4 – 4.4 ppm region. Hence, to calculate the conversion in the 91% conversion for example (Figure 2.19 - C, Table 2.10, Entry C), all the protons in the spectra were normalised to 100 and the olefin region showed 2.25 out of 100. This means that in this total 100 protons there is 2.25 refer to the olefin and so 6.75 protons (3 * 2.25) in 3.4 – 4.4 ppm area refer for non-dihydroxylated unit. Hence, the total protons for the non-dihydroxylated unit are 9, so the rest 91 protons refer to dihydroxylated unit.

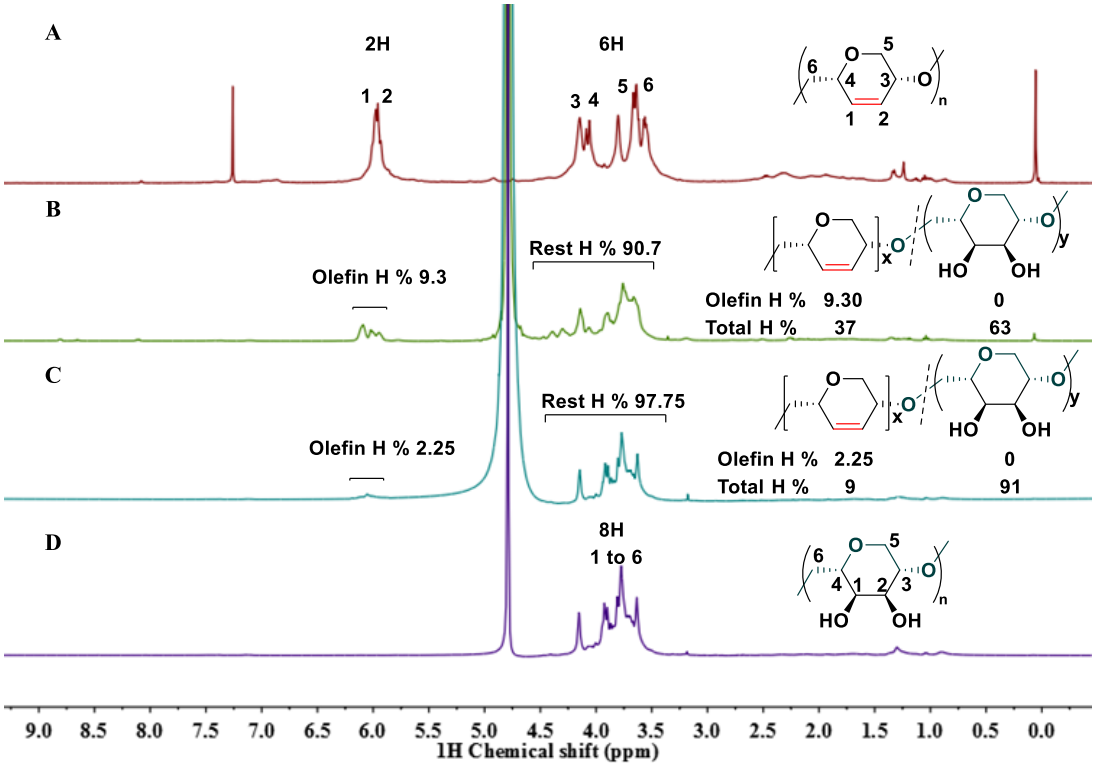


Figure 2.19 ^{1}H-NMR (500.2 MHz) of *(R)*-FCPE in *CDCl*$_3$ (A), 63 % (B) 91 % (C) and ≥99% (D) dihydroxylation of *(R)*-FCPE in *D*$_2$*O*.

Table 2.10: Controlled dihydroxylation to form *cis*-PEGose**.**

Entry	[Olefin]: [NMO]	^{1}H-NMR olefin integration %	Con.(%)[a]	Soluble in	Insoluble in
A	0:0	25	-	DEE to MeOH	-
B	1:0.7	9.30	63	Acetone	EtOAc, CH_2Cl_2
C	1:0.9	2.25	91	DMF, MeOH	Acetone
D	1:1.1	0	>99	H_2O, DMSO	DMF

[a] Determined by ^{1}H-NMR spectroscopy of olefin peaks integration to the polymer peaks.

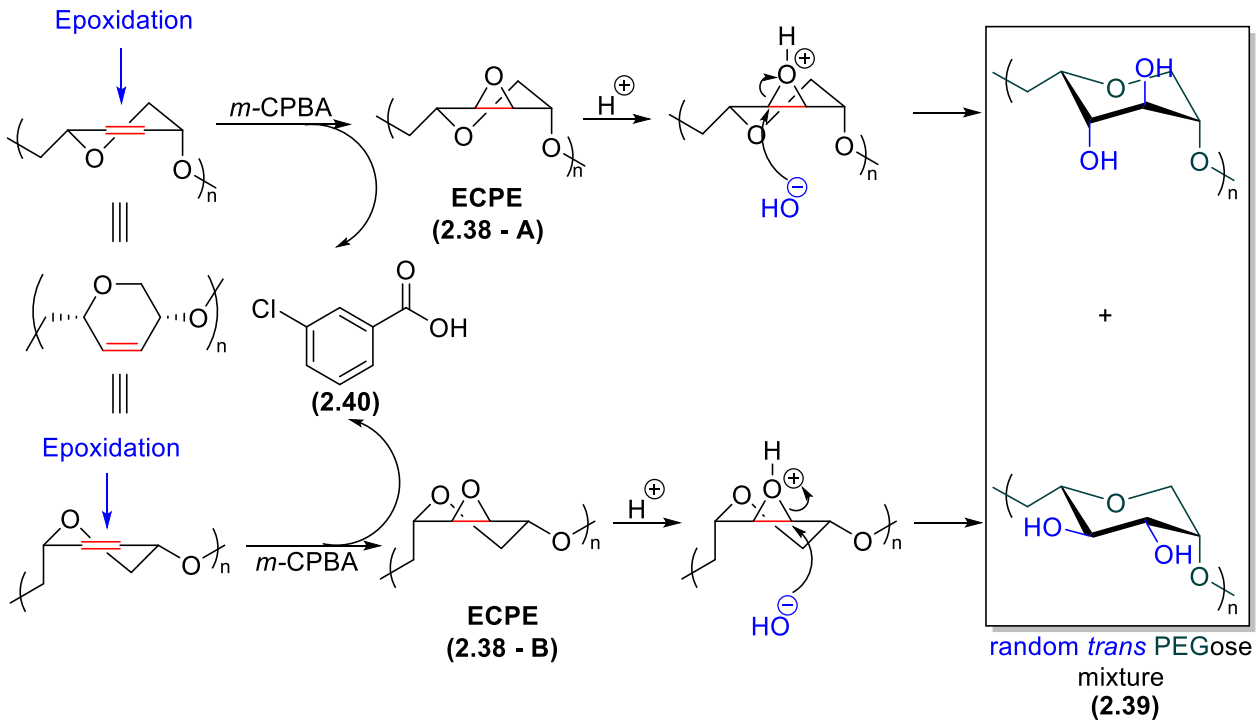
While the fully dihydroxylated polymer (**2.36**) was not soluble in dimethylformamide (DMF), this 91% dihydroxylated polymer was easily soluble in DMF and MeOH. To broaden the solubility range of the partially dihydroxylated PEGose (**2.35**), the ratio of PEGose to FCPE was reduced to around 65% by reducing the NMO loading to 0.7 equivalent (B, Table 2.10 and Figure 2.19). This polymer showed a solubility in less polar solvents such as acetone.

PEGose is a water-soluble polyether like polyglycerol (PG) but with a stereocontrolled and cyclopolymeric structure. Polyglycerol is an aliphatic polyether exhibiting good chemical stability and inertness under biological conditions. Its biocompatibility is similar to that of poly(ethylene oxide) (PEO).[9] Thus, PEGose would potentially have these properties, which make it an attractive polymer for biomedical application.

2.9.2 Epoxidation

While dihydroxylation of (*i*)-FCPE afforded *cis*-diols, hydrolysing the epoxide derivative would give *trans*-diols. The olefin group in (*i*)-FCPE can be epoxidised using a common peroxycarboxylic acid such as *meta*-chloroperoxybenzoic acid (*m*-CPBA). Epoxidation should also occur on the less hindered side of the ring of (*i*)-FCPE to give epoxide cyclopolyether (ECPE) (**2.38**) (Scheme 2.18). Then, by hydrolysing this new epoxide, *trans* diols of PEGose (**2.39**) can be obtained. The epoxidation reaction conditions were optimised on (*a*)-PEB using *m*-CPBA (60%, 3eq.) in DCM at ambient temperature. While these conditions afforded the epoxide derivative of (*a*)-PEB, these conditions did not yield ECPE (**2.38**). The isolated polymer was not soluble in chloroform, and it was soluble only in polar solvents such as water and dimethyl sulfoxide (DMSO). The ^{13}C-NMR spectrum showed a broad

peak, overlapping resonances (δ 81- 65), which does not reflect the stereoselectivity of the epoxidation. Besides, the ^{1}H-NMR spectrum (Figure 2.20) did not show the new protons of the desired epoxide. All these indicated that the isolated polymer at the end of the reaction was probably *trans* PEGose (**2.39**), which is a mixture of the two diastereomers produced. It seems that ECPE (**2.38 A and B conformations**) were not stable at these conditions due to the high ring strain of the epoxide-ring monomer unit. The acidity of *m*-chlorobenzoic acid (**2.40**), which is the by-product of *m*-CPBA after epoxidation, in the presence of the water, come from *m*-CPBA (60%), promoted the hydrolysis of the epoxide (**2.38**) to diols (**2.39**) during the epoxidation reaction. The ^{13}C-NMR showed a very broad peak between 60 -83 ppm.



Scheme 2.18 Epoxidation and an acid hydrolysis of (*R*)-FCPE to random *trans* diols of PEGose.

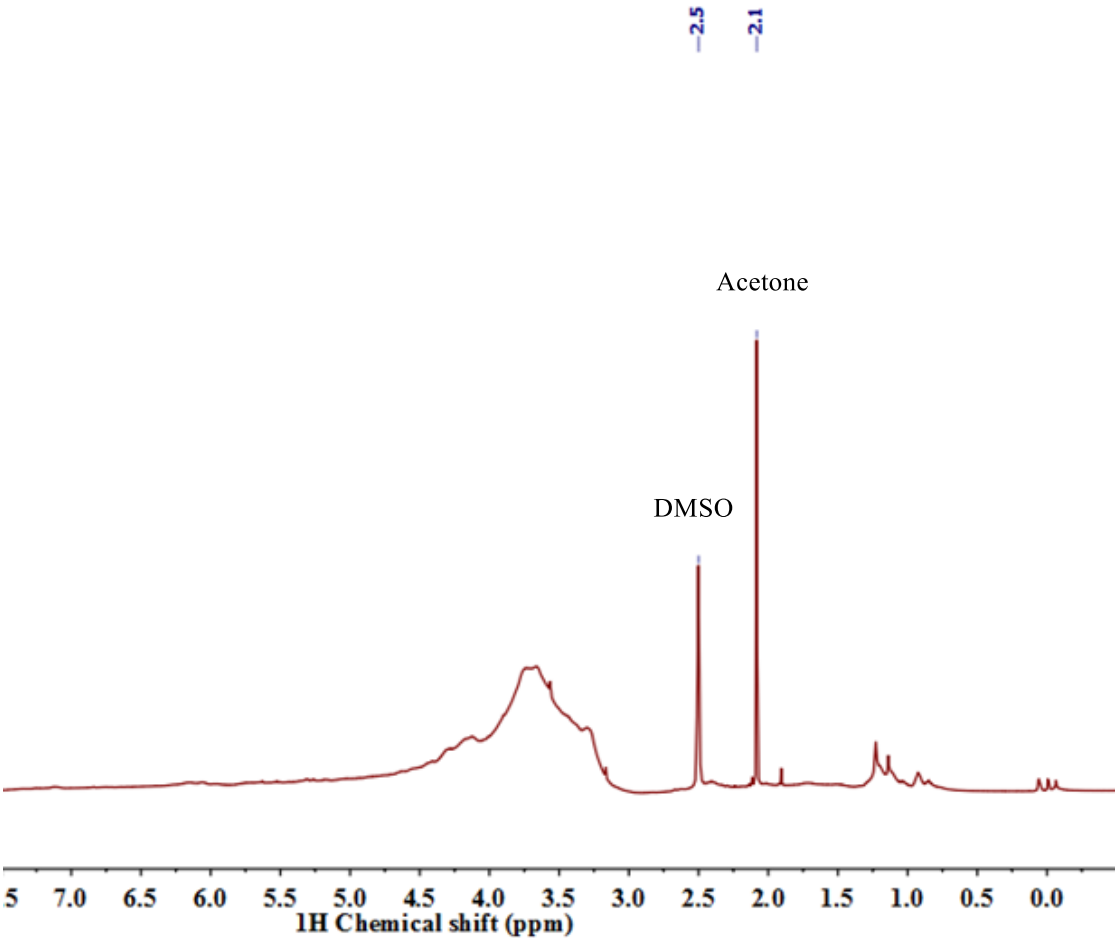


Figure 2.20 ^{1}H-NMR (*DMSO-d6*, 500.2 MHz) of the hydrolysis product of (*R*)-RCPE.

2.10 Stereoregularity of FCPE and PEGose

2.10.1 Stereocomplex

Polymers with opposite configurations or complementary chiralities can cocrystallise in stereocomplexes in their mixtures and stereoblock copolymers. In the blends of complementary polymer enantiomers, both the homocrystallisation of stereocomplex between complementary enantiomers and individual enantiomers and can take place.[57] In contrast to conventional homocrystallisation, stereocomplex crystallisation is governed by stronger intermolecular interactions such as stereoselective *v*an der Waals forces, hydrogen bonds, or electrostatic forces. This generally leads to tighter and energy-favourable packing of polymer chains in stereocomplexes than that observed in homocrystallites. Owing to the unique crystalline structure, the stereocomplexed materials often exhibit stronger physical properties than their homocrystalline counterparts.[58] While the atactic polyethers are amorphous, many isotactic polyethers

are semicrystalline thermoplastics, which increases their range of possible applications. For example, atactic PPO is amorphous (T_g = -70 °C), whereas isotactic PPO (*i*-PPO) is a semicrystalline material (T_m = 67 °C).[59]

Since (*i*)-FCPE showed in ^{13}C-NMR spectroscopy a highly ordered stereostructure, we hypothesised that a mixture of (*R*)-FCPE and (*S*)-FCPE would promote a stereocomplex structure (Figure 2.21).

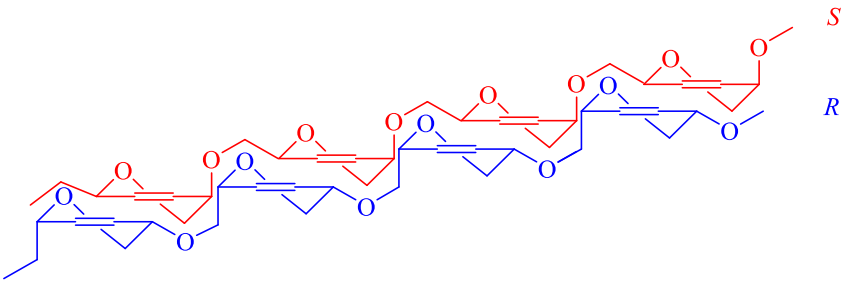


Figure 2.21 Possible (*i*)-FCPE chains packing of complementary chiralities to promote stereocomplex formation.

While there are several methods for mixing polymers that have opposite configurations or complementary chiralities to promote stereocomplex formation,[57] two common methods have been used; slow evaporation of a mixture solution (method one)[60] and precipitation into a non-solvent (method two).[57] To achieve that, 50 mg each of (*R*)-FCPE ($M_{n,GPC}$ = 2600, Đ 1.19) and (*S*)-FCPE ($M_{n,GPC}$ = 2700, Đ 1.24) were dissolved in dichloromethane (2 mL) and mixed together by shaking in a small vial. In method one, the top of the vial was then covered with parafilm, punctured with one hole, and the solvent was allowed to evaporate slowly and completely. After 14 days, the material was dried in vacuo to ensure all solvent was removed. In the second formation method, the previous polymers mixture (4 mL in DCM) was precipitated in cold diethyl ether (-70 °C, 30 mL), filtered and dried in vacuo.

While method one gave a sticky material, method two afforded a solid material (Figure 2.22). These two obtained materials were compared by differential scanning calorimetry (DSC) and powder X-ray diffraction. The DSC data showed that both mixtures have higher glass transition temperatures than the individual enantiopolymers. While the T_g of (*R*)-FCPE and (*S*)-FCPE were around -11 °C, the mixture showed a T_g around +50 °C and +43 °C for methods one and two, respectively (Table 2.11). However, no crystallization peaks (T_c) or melting peaks (T_m) were observed in both mixtures.

Figure 2.22 Solid material of mixture (*R*)-FCPE and (*S*)-FCPE obtained by method two.

Table 2.11: Glass transition temperature of (*R*)-FCPE and (*S*)-FCPE and their mixture.

Polymer[a]	Formation	T_g (°C)
(*R*)-FCPE	Evaporation	-10.5
(*S*)-FCPE	Evaporation	-11.1
Mixture	Slow evaporation	+49.5
Mixture	Precipitation	+42.7

[a] (*R*)-FCPE ($M_{n,GPC}$ = 2600, Đ 1.19) and (*S*)-FCPE ($M_{n,GPC}$ = 2700, Đ 1.24).

The X-ray diffraction (XRD) spectra (Figure 2.23) did not exhibit sharp diffraction peaks. The XRD of both mixtures showed broad peaks, which confirm the amorphous nature of these two materials.

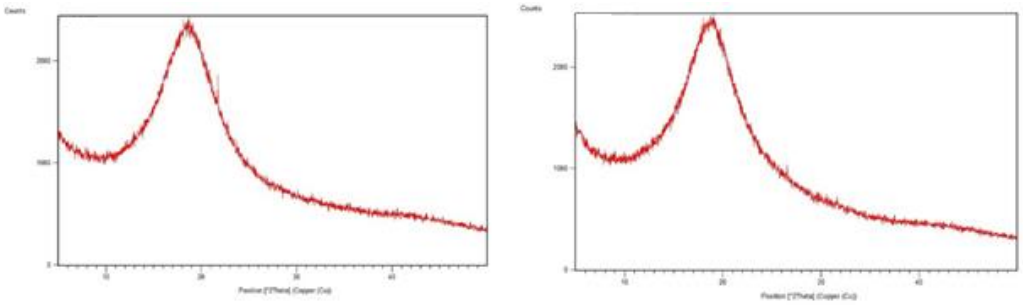


Figure 2.23 X-ray diffraction spectra of method one (left) and method two (right).

2.10.2 Helicity

Synthetic polymer chains usually have unlimited random chain conformations, primarily due to the free rotation around σ-bonds of the polymer backbone. However, the intramolecular non-covalent bonding forces induce the macromolecule to fold into a specific conformation. This is governed by the interplay of multiple molecular recognition processes such as hydrogen-bonding, *v*an der Waals, electrostatic and solvophobic interactions.[61-62] Nowadays, many researchers are developing polymers that can adopt specific conformations to control the physical and the thermal properties of macromolecules which in turn expand their applications. The precisely ordered stereostructures of natural polymers such as proteins, glucans and genes inspired polymer architects to design highly ordered stereostructures of synthetic polymers. In such systems, the helix is often found among the most fundamental structures of the natural polymer chain and plays important roles in realising biological activities.[63] The stereocontrolled helix macromolecules attract interest of synthetic polymer scientists due to their broad applications including molecular recognition, chiral chromatography, sensory functions and enantioselective catalysis. However, preparation of artificial helical polymers is a great challenge to the polymer chemists. By introducing chirality into synthetic molecules, helical textures in different length scales can be obtained by self-assembling through interplay secondary interactions. Helical polymers can be classified into two types: static and dynamic helical polymers, depending on the nature of the helical conformation. Static helical polymers possess stable helical conformations with high helix inversion barriers and dynamic helical polymers adopt an alternating sequence of left- and right-handed helices separated by helical reversal with low helix inversion barriers (Figure 2.24).[63-64]

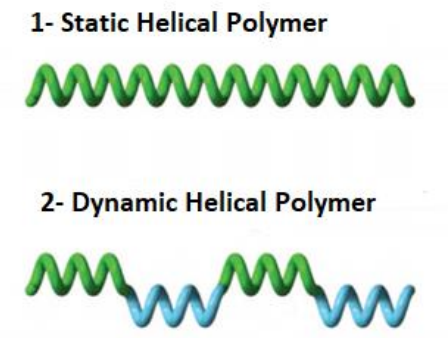
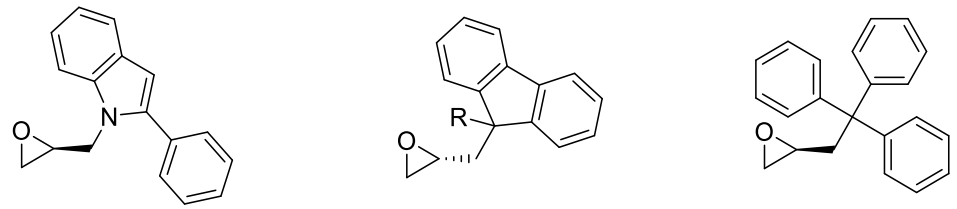


Figure 2.24 Two types of helical polymers and their representative structures.

In principle, optically active static helical polymers can be synthesised by either the polymerisation of optically active monomers or the helix-sense-selective polymerisation of achiral or prochiral monomers using chiral initiators or catalysts, when the helix inversion barriers are sufficiently high.[64] The key point in this kind of polymerisation is to prevent the random conformation change by creating either rigidity in the main chain or steric repulsion of the side groups. So far, huge amounts of synthetic polymers which keep a single-handed helical conformation in solution have been synthesized from acrylamides,[66] styrenes,[67] aldehydes,[68] isocyanates,[69] isocyanides,[70] acetylenes,[71] and so on. There is a common characteristic that the repeated unit of the backbone contains only two atoms and the atoms bearing a bulky pendant group responsible for forming helical conformation are isolated from each other only by one methylene.[72] However, ROP of a mono-substituted epoxide will result in a longer bridge (methoxy) between the pendent groups. Thus, the flow characteristics of polyethers are the lowest of any of the elastic materials, which result in a difficulty for forming a helical structure. Recently, a few optically active helical polyethers were reported by ROP of enantiopure epoxides bearing a bulky pendent group such as (4,4,4-triphenyl-1-butene oxide (TPBO),[73] (3-(9-alkylfluoren-9-yl)propene oxide)[72] and 1-(oxirane-2-ylmethyl)-2-phenylindole (Figure 2.25).[74]



1-(Oxiran-2-ylmethyl)-2-phenylindole **(2.41)**

3-(9-alkylfluoren-9-yl) propene oxides **(2.42)**

TPBO **(2.43)**

Figure 2.25 Three enantiopure bulky functional epoxides were used to make helical polyethers.

While several techniques are used for the structural analyses of helical polymers, evidence for a helix formation of synthetic polymers is usually obtained by circular dichroism (CD). CD spectroscopy is a kind of light absorption spectroscopy that measures the difference in absorbance of right- and left-circularly polarised light by a substance. It has been shown that CD spectra between 260 and approximately 180 nm

can be analysed for the different secondary structural types such as alpha-helix, parallel and antiparallel beta-sheet, turn, and others.[64]

(*i*)-FCPE and (*R*,*R*) *cis* PEGose showed in the ^{13}C-NMR spectra highly ordered stereostructures and we hypothesised that these polymers would have an optical activity. Circular dichroism spectra of these polymers' solutions were taken at room temperature between 260 and approximately 180 nm. It was not possible to measure in a lower wavelength due to the limitations of the instrument. Two scans for each sample were collected at a speed of 20 nm/min.

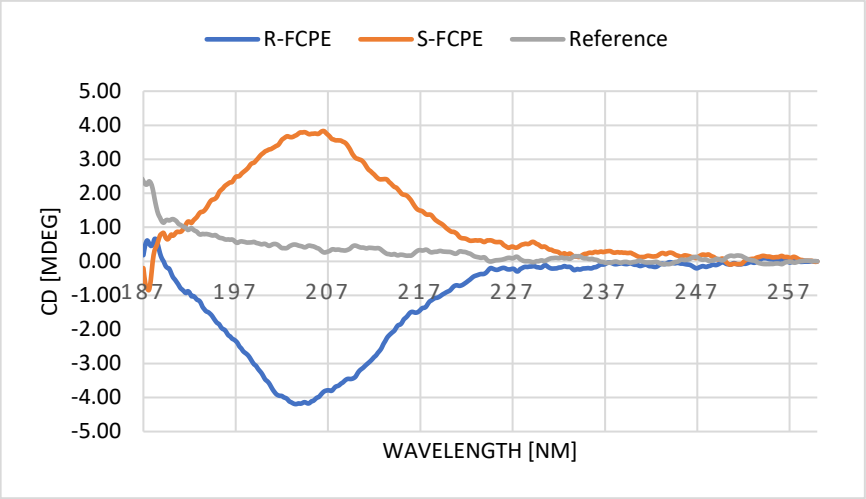


Figure 2.26 Circular dichroism of (*R*)-FCPE and (*S*)-FCPE in methanol at 1 mg/mL using methanol with traces of the used catalysts as a reference.

CD spectra of methanol solutions of (*S*)-FCPE and (*R*)-FCPE at 1 mg/ mL showed that these two polymers were mirror images of each other and promoted the formation of an α-helical structure in solution (Figure 2.26). While (*R*)-FCPE has a negative Cotton effect, (*S*)-FCPE has a positive Cotton effect at 204 nm wavelength corresponding to right-handed- and left-handed-helical segments, respectively. This absorbance probably refers to the $\pi \rightarrow \pi^*$ transition of the olefin of the unsaturated ring of (*i*)-FCPE.

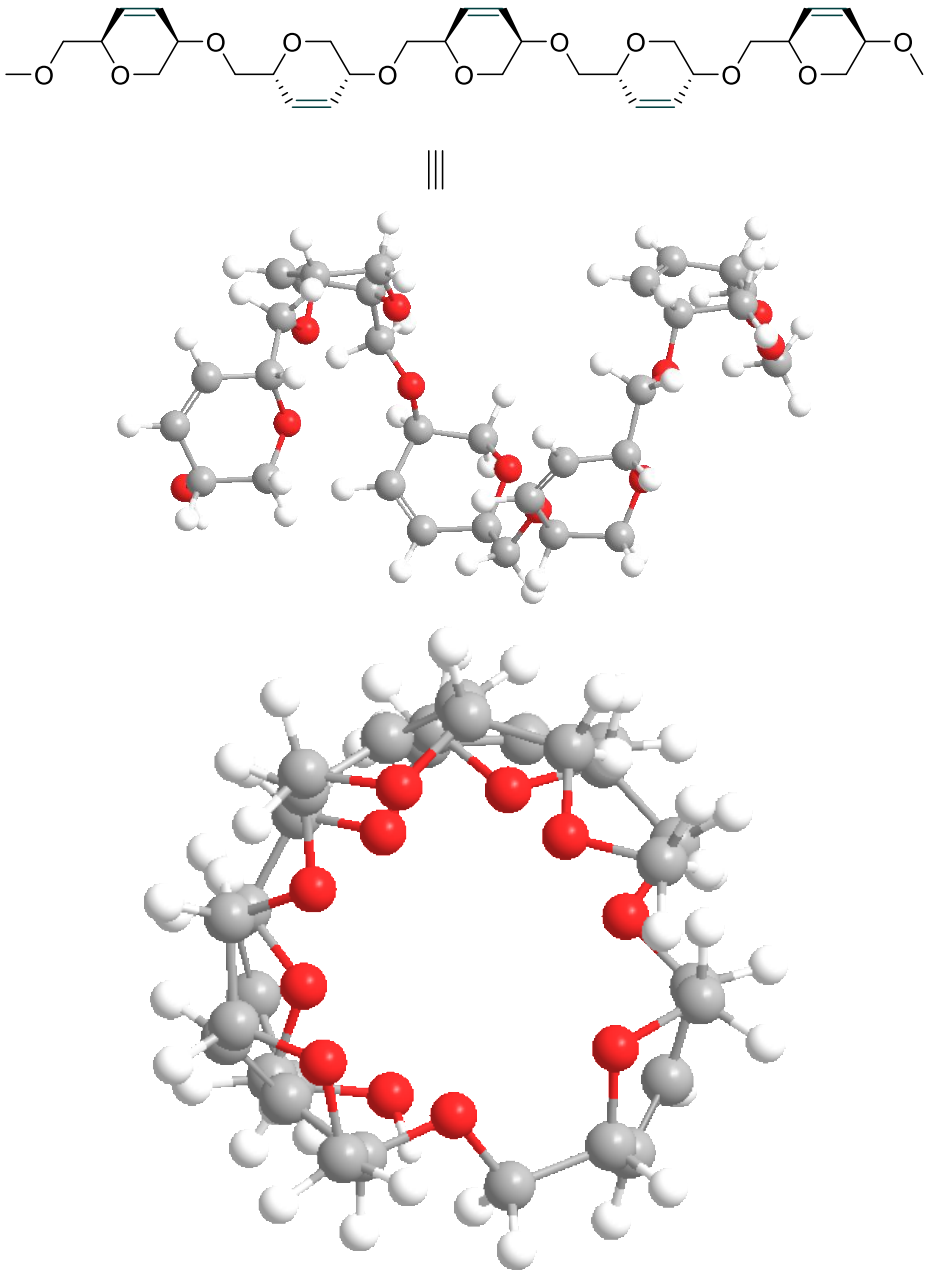


Figure 2.27 Model of (*R*)-FCPE with ChemBio3D Ultra 14.0 software, 2D (top), 3D side face (middle), 3D front face (bottom).

In order to confirm the stability of the helical conformation of (*i*)-FCPE further, modelling was performed with ChemBio3D Ultra 14.0 software. The structure of (*R*)-FCPE in the software took on a beautiful helical structure (Figure 2.27) and this probably comes from the rigidity of the unsaturated cyclic monomer units.

Although dihydroxylation of (*R*)-FCPE will saturate the π-bond of the monomer unit of FCPE and this would reduce the rigidity of the polymer backbone, the secondary

structure of (*R,R*) *cis* PEGose solution in water at neutral pH (1mg/ mL) also showed a negative Cotton effect corresponding to a left handed-helical structure (Figure 2.28). While amylose, $(C_6H_{10}O_5)_n$, and PEGose,$(C_6H_{10}O_4)_n$ have similar monomer units, PEGose is connected with an additional methylene bridge, which gives more flexibility to the polymer backbone. Surprisingly, (*R,R*) *cis* PEGose and amylose have the same prominent negative bands at λ = 182 nm (Figure 2.28),[75] which shows that PEGose has an extended pseudo helical structure similar to amylose.

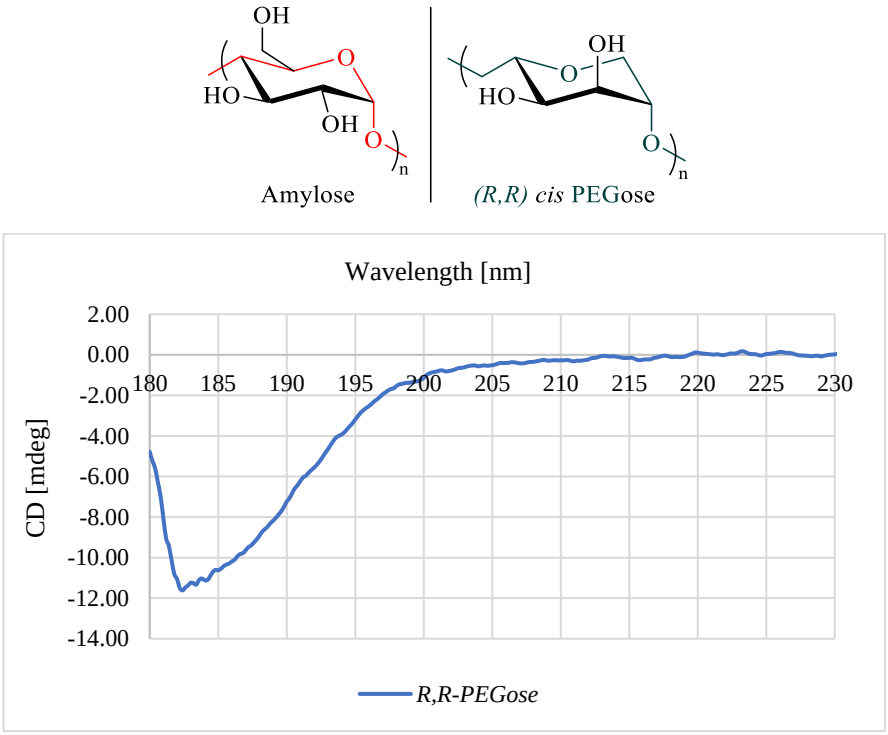


Figure 2.28 Circular dichroism of (*R,R*) *cis* PEGose in water.

While amylose is poorly soluble in water and forms suspensions, in which its helicity is preserved,[76] (*R,R*) *cis* PEGose is a readily water-soluble synthetic polymer with conformational stability in aqueous solution, which is important with regard to biological applications.

On the other hand, non-stereocontrolled atactic PEGose (**2.44**), which has been obtained by osmium dihydroxylation of atactic FCPE (**2.30**) or the epoxidation product of *(R)*-FCPE (**2.39**) did not give rise to circular dichroism spectra. The positive rise of the polymers was close to the reference rise which confirms that these polymers do not have specific conformations (Figures 2.29 and 2.30).

atactic PEGose (**2.44**) random *trans* PEGose (**2.39**)

Figure 2.29 Chemical structure atactic PEGose (**2.44**) and (*R*,*R*) random *trnas* PEGose (**2.37**).

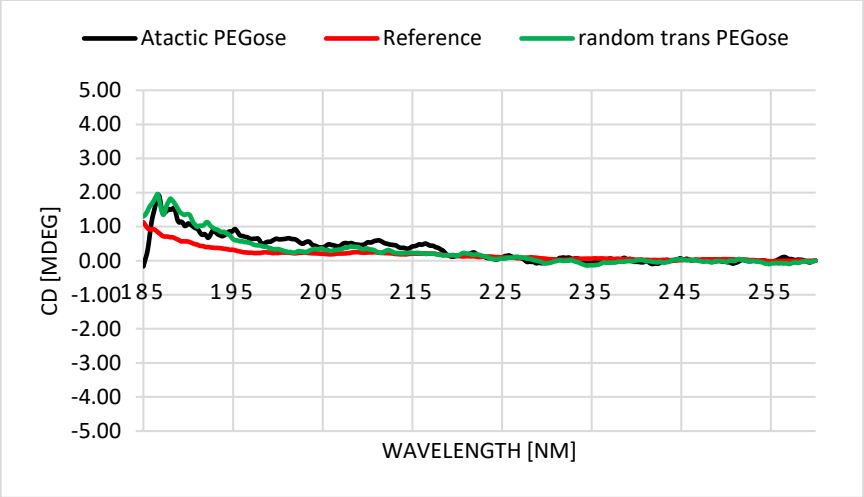


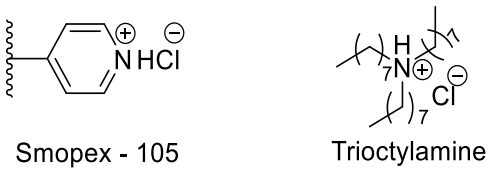
Figure 2.30 Circular dichroism of atactic PEGose (**2.44**) and random trans PEGose (**2.39**) in water at 1 mg/mL using water with traces of the used catalysts as a reference.

This validates the hypothesis that the helical properties of *(R,R) cis* PEGose and (*i*)-FCPE comes from the stereocontrolled structure of these polymer backbones as well as the stereocontrolled of the *cis*-diol groups.

2.11 Metal residues and purification

Unfortunately, FCPE and PEGose preparation involved toxic metal derivatives of ruthenium and osmium. It is desirable to avoid these metal residues for eventual biomedical application, since they are highly toxic even in low residual amounts in the final polymers.[77-76] All the polymers made in this chapter were purified using size exclusion chromatography (Sephadex), which can remove all the small molecules of catalysts and reagents from the polymer mixture. However, due to the bulky nature of polymers, some impurities and metal residues could be stuck on their surface. For this reason, the metals residues of Ru and Os in PEGose were measured by inductively coupled plasma mass spectrometry (ICP-MS) (Table 2.12). While the level of Ru was

reduced significantly by 94% after using a Sephadex column, Os traces decreased by 31% only. For this reason, PEGose was further purified to reduce the Os residues level. The common commercial scavenger of osmium tetroxide and other negatively charged metal species is a vinyl pyridine grafted polyolefin (Smopex-105 – **2.45**) as the metal ions can be complexed by the pyridine hydrochloride side group. Following this principle, a novel cheap scavenger was made for this purpose from trioctylamine hydrochloride (TOAHC) (**2.46**, Figure 2.31).



Smopex - 105 (2.45)

Trioctylamine hydrochloride (2.46)

Figure 2.31 Structures of vinyl pyridine grafted polyolefin (Smopex-105) and trioctylamine hydrochloride.

This novel scavenging method, employing cheap amine hydrochloride, was extremely efficient with 95% removal of osmium residues. The efficiency was also seen in the colour of the PEGose suspension. The PEGose solution was black after Sephadex column purification due to this high level of osmium residues. After using this new scavenger, the colour became pale yellow (Figure 2.32).

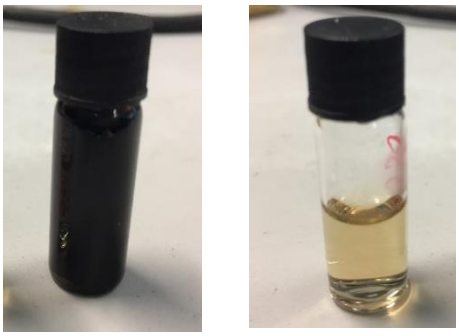


Figure 2.32 The PEGose solution in water before (left) and after (right) using our TOAHC as a scavenger.

Table 2.12: The levels of Os and Ru metals of (*R,R*) *cis* PEGose.

Metal	Initial (ppm)	After column (ppm)	Purification efficiency (%)	After extraction (ppm)	Purification efficiency (%)
Os	$6.7*10^3$	$4.6*10^3$	31	215	95
Ru	$72.6*10^3$	$4.8*10^3$	94	-	-

2.12 Conclusion

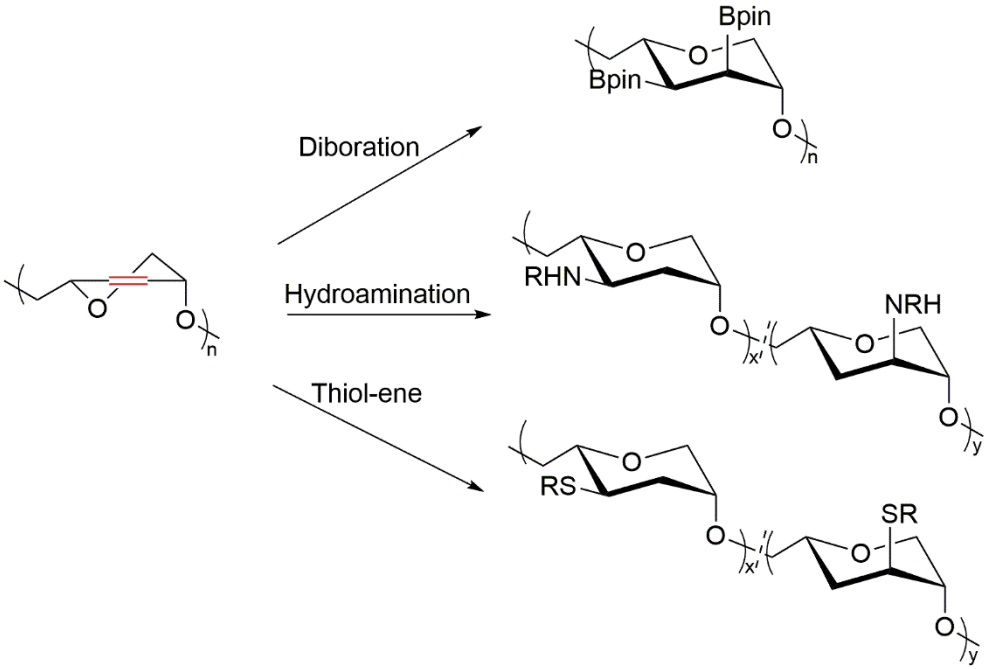
We have shown that RCM of linear, stereoregular polyether with pendent olefins can be used to prepare cyclopolymers with excellent control over the ring size. The product was dependent on the reaction parameters; concentration, temperature, time, catalyst type and loading, and the stereoregularity of the starting polymer. The reaction was divided into a fast metathesis and a slow remetathesis stage. This assumes that olefins in PEB behaved as Type I olefins. The isotactic linear PEB leads, after RCM, to a functionalisable cyclopolyether (FCPE) with well-defined *cis* substitution patterns. Both (*S*)-FCPE and (*R*)-FCPE polymers were mirror images of each other and showed helical conformation structures in solution. The helicity is highly dependent on all the stereogenic centres of the polymers.

Further functionalization of the latent olefin groups by dihydroxylation provides sugar-like structures with a poly(ethylene glycol) backbone that leads to a new PEGose architecture. By taking advantage of the diastereoselectivity of the subsequent dihydroxylation reaction, we were able to create a cyclopolymer where the configuration of all the stereogenic centres is controlled, and which mimics naturally occurring amylose. Also, the degree of the dihydroxylation was controlled to broaden the solubility of the resulting polymer and to leave olefin sites for further functionalisation. This new platform offers significant potential for drug conjugation, biomedical mimicry and paves the way to afford cyclopolymers with a wide range of functional groups.

2.13 Future work

Since FCPE is functionalisable, then it is a great platform for cyclopolyethers with a wide range of functional groups. First, treatment of the olefin of FPCE with *bis*(pinacolato)diboron[79] would lead to the corresponding diborated polymer. The versatile boronate functional group can be transformed into hydroxyl[80] or amino[81] groups by oxidation reactions, or into *bis*(pentafluorophenyl)boron groups.[82] This diborated polymer can be converted into PEGose with hydrogen peroxide under basic conditions, which provides an alternative synthesis of PEGose not involving toxic osmium tetroxide. Also, thiol-ene click reactions[83] with diverse thiols will lead to thio

polysaccharide mimics (ThioPEGose), while hydroamination[84] will give access to a range of amino-polysaccharide mimics (AminoPEGose).



Scheme 2.19 A representative scheme for possible functionalisations of functionalisable cyclopolyether.

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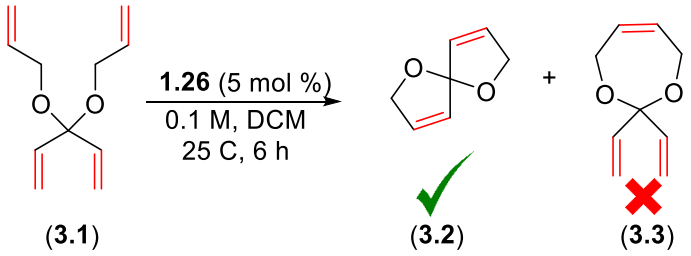
Chapter 3. Starting Polymers for Size-Selective-RCM

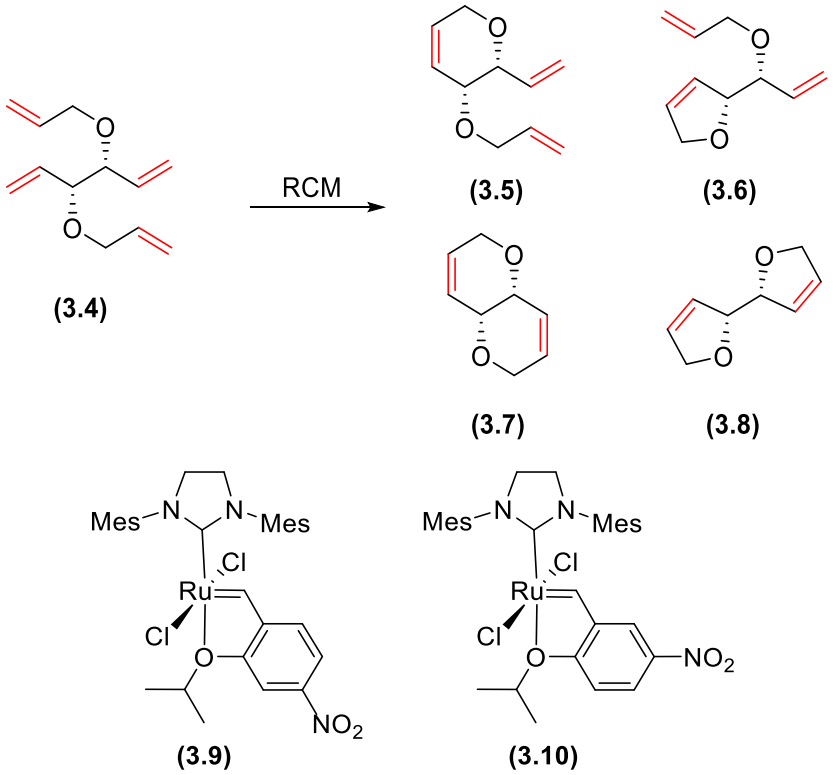
3.1 Introduction

As we noticed in chapter two, the RCM reaction is under thermodynamic control, but initial kinetic products are formed at the onset of the reaction. These kinetic products reenter the catalytic cycle to form the most thermodynamically stable rings. This equilibrium between the kinetic and the thermodynamic products can be perturbed through a variety of parameters to overturn the product ratios in favour of the desired RCM product. The product distributions are governed by concentration, catalyst, olefin substrate, reaction time and temperature. For example, high dilutions are required to limit intermolecular cross-linking and if dilutions are insufficient, the equilibrium will favour cross-metathesis over the desired RCM products.[1,2] However, RCM may not only compete with olefin cross-metathesis but also with itself when the reaction can produce two different ring-sizes. For example, tetraalkene (**3.1**) can undergo ring-closing metathesis through two modes leading to two different products; (**3.2**) and (**3.3**). However, the ring cyclisation proceeded with complete selectivity to the more thermodynamically stable product of spirocyclic acetal (**3.2**) with no detectable quantity of the 7-membered-cyclic acetal (**3.3**) (Scheme 3.1).[3]



Scheme 3.1 RCM of tetraalkene (**3.1**) to afford exclusively spirocyclic acetal.

Control of ring-size selectivity has been reported in several works[4-9] and the best example is the work that was reported by Schmidt *et al.*[10] When (*3R,4R*)-3,4-*Bis*(allyloxy)hexa-1,5-diene (**3.4**) was treated by metathesis catalysts under different conditions, four cyclic products were observed at different ratios (Scheme 3.2).

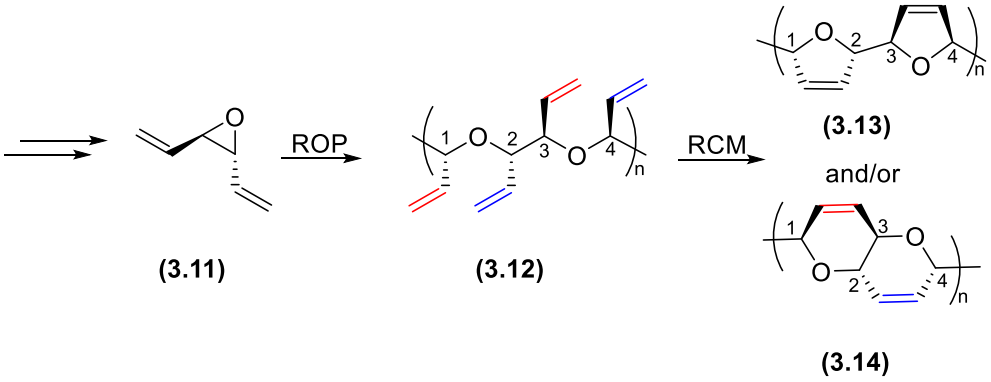


Scheme 3.2 Four cyclic-products from RCM of **3.4** using metathesis catalysts **1.28**, **1.29**, **3.9** and **3.10**.[10]

bis-Dihydrofuran (**3.8**) was the exclusive product when 1st generation Grubbs catalyst (**1.28**) was used at 20 °C. However, changing only the catalyst to **1.29**, **3.9** or **3.10** gave different ratios of the four cyclic products. Given the high selectivity obtained with the least reactive catalyst (**1.28**), one might speculate that kinetic control is the origin of the perfect ring-size selectivity. To confirm this, the ring-closing metathesis reactions were repeated in refluxing toluene. Under these conditions, all used catalysts gave full conversion to bicyclic products (**3.7**) and (**3.8**) and the amount of six-membered product, *bis*-dihydropyran (**3.7**), increased slightly. Also, conducting the reactions under an atmosphere of ethylene increased the ratio of the six-membered product (**3.7**). This confirmed that *bis*-dihydrofuran (**3.8**) was the kinetic product and the reaction at higher temperatures or under ethylene facilitated a ring-opening metathesis of this kinetic product and eventually resulted in a higher percentage of (**3.7**) as a thermodynamically stable product.[10]

3.2 Aims and objectives

Various tri- and tetraenes have been subjected to ring-size selective - double RCM reactions using different catalysts and conditions. However, using this principle on polymers has not been reported yet. This chapter aims to explore the synthesis of a starting polyether with pendent olefins that is suitable for ring size-selective - double RCM. The ideal polymer for this reaction is poly(divinyl-oxirane) (PDVO- **3.12**), which can be obtained by ring-opening polymerisation of enantiopure *trans*-divinyl oxirane (**3.11**).



Scheme 3.3 ROP of *trans* divinyl oxirane (**3.11**) to make divinylPEG (**3.12**); a starting polymer for size-selective by RCM.

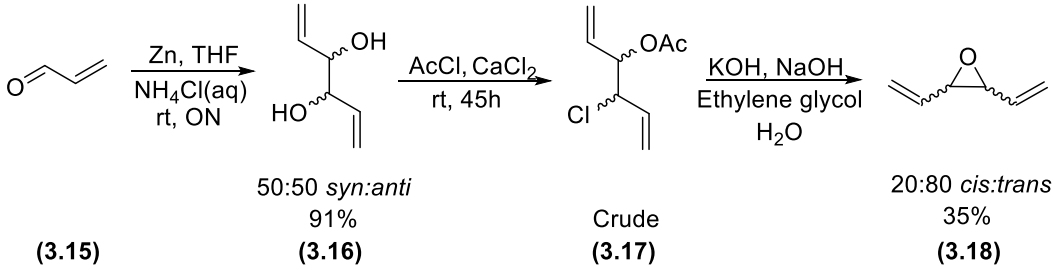
RCM of the starting polymer, PDVO - **3.12**, has several possible outcomes. If vinyl groups separated by three carbon atoms react (one red olefin at C1 with one blue olefin at C2), a cyclopolymer consisting of 2,5-dihydrofuran units will be formed (DHF polymer - **3.13**). If two red olefins separated by four carbon atoms react, followed by further RCM of the neighbouring two blue olefins, the repeating unit encompasses two fused 3,6-dihydropyrans (DHP polymer – **3.14**). The outcome can be controlled by changing the reaction parameters; concentration, catalyst, time and temperature.

3.3 Synthesis of divinyl oxirane

3.3.1 Racemic *trans*-divinyl oxirane

Although enantiopure *trans*-divinyl oxirane was required to afford an isotactic polymer of poly(divinyl-oxirane) (**3.12**), racemic *trans* divinyl oxirane (**3.18**) was prepared first to investigate the ROP conditions of this monomer. Epoxide (**3.18**) was prepared following the protocol that Passannante *et al.* used (Scheme 3.4).[11] 1,5-

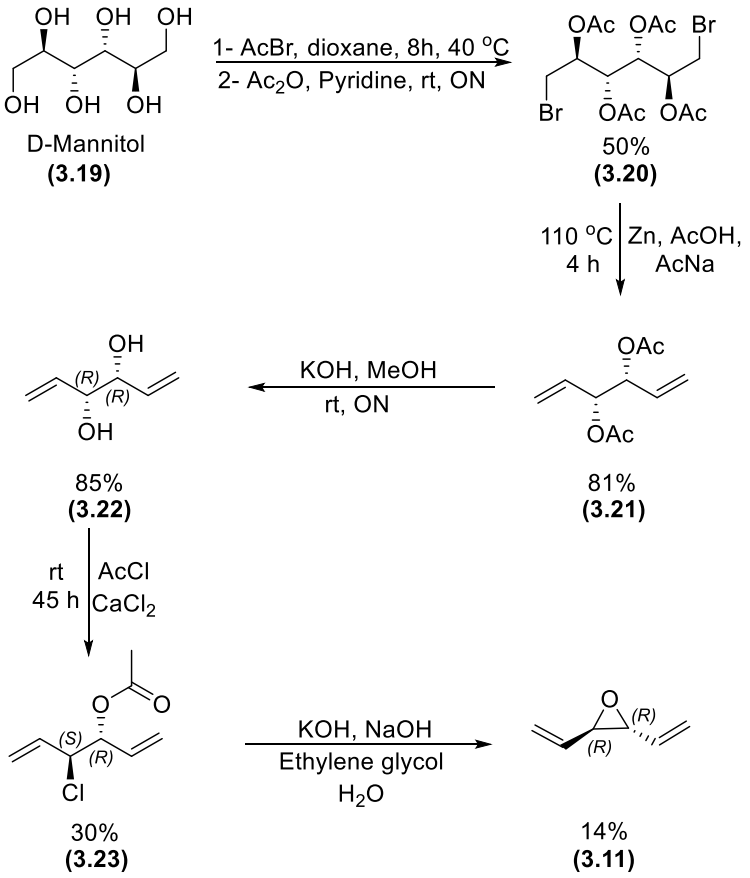
Hexadiene-3,4-diol (**3.16**) was conveniently prepared by the pinacol coupling of acrolein (**3.15**) promoted by zinc.[12] Then, 1,5-hexadiene-3,4-diol (**3.16**) was converted into 3-chloro-4-acetoxy-l,5-hexadiene (**3.17**) by treatment with calcium chloride ($CaCl_2$) in neat acetyl chloride (AcCl). The ring formation from the chloroester derivative can be accomplished under basic conditions. The product was distilled and trapped in a receiver cooled by liquid nitrogen to give *cis*- and *trans*-divinyl oxiranes (**3.18**) as a 20:80 mixture of diastereomers – *cis: trans*. The ratio was determined by ^{1}H-NMR spectroscopy (400 MHz) using the relative integration values of the oxirane ring protons at 3.53 (*cis*, J_{HH} = 6.5 Hz, 20%), 3.21 (*trans*, J_{HH} =8.2 Hz, 80%) (See Figure 3.1 – top spectrum).



Scheme 3.4 Three-steps reaction for preparing racemic divinyl oxirane (**3.18**) from acrolein.

3.3.2 Enantiopure *trans*-divinyl oxirane

Synthesis of enantiopure *trans*-divinyl oxirane (**3.11**) has not been reported in the literature yet. However, it can be synthesised from (*3R,4R*)-3,4-dihydroxy-1,5-hexadiene (**3.22**), which was synthesised from D-mannitol (**3.19**) in three steps, following the protocol that was reported by Schmidt *et al.*[10] To this end, D-mannitol was first treated with acetyl bromide (AcBr) for bromination of the primary alcohols, followed by acetylation of the remaining secondary hydroxy groups to give **3.20**. The product underwent reductive elimination of bromide and acetate, as previously described by Burke *et al.*,[13] to give the diacetate (**3.21**). Then, the deacetylation was achieved by methanolysis in the presence of a catalytic amount of aqueous KOH, rather than K_2CO_3. Thus, **3.22** becomes available from D-mannitol in three steps in multi-gram quantities in 34% overall yield (Scheme 3.5). Then, **3.22** was converted into (*3S*)-chloro-(*4R*)-acetoxy-l,5-hexadiene (**3.23**) using acetyl chloride and calcium chloride (Scheme 3.5).



Scheme 3.5 Five-steps reaction for preparing enantiopure *trans*-divinyl oxirane (**3.11**) from D-mannitol.

Lastly, enantiopure *trans*-divinyl oxirane (**3.11**) was obtained by an intramolecular S_N2 displacement of chloride of **3.23**. The mechanism of converting **3.22** to **3.23** is not clear. However, since the ^{1}H-NMR spectrum (Figure 3.1) of the epoxide (**3.11**) showed only peaks which correspond to *trans*-divinyl oxirane, this means that the two stereogenic centres of **3.23** were (*S*) and (*R*). One equivalent of AcCl converted one hydroxyl to an acetyl group with retention of the configuration of this stereogenic centre (*R*). This means that the nucleophilic substitution of the other hydroxyl by chlorine converted the configuration of this stereogenic centre from (*R*) to (*S*) by an S_N2 mechanism.

Traces of dioxane and diethyl ether were also distilled during the collection of **3.11**. The re-distillation of **3.11** was not possible as the collected crude material amount was around 0.5 g. For this reason, we started developing the ROP of *cis*- and *trans*-divinyl oxirane (**3.18**), since it can be prepared in fewer steps and a higher yield than **3.11**.

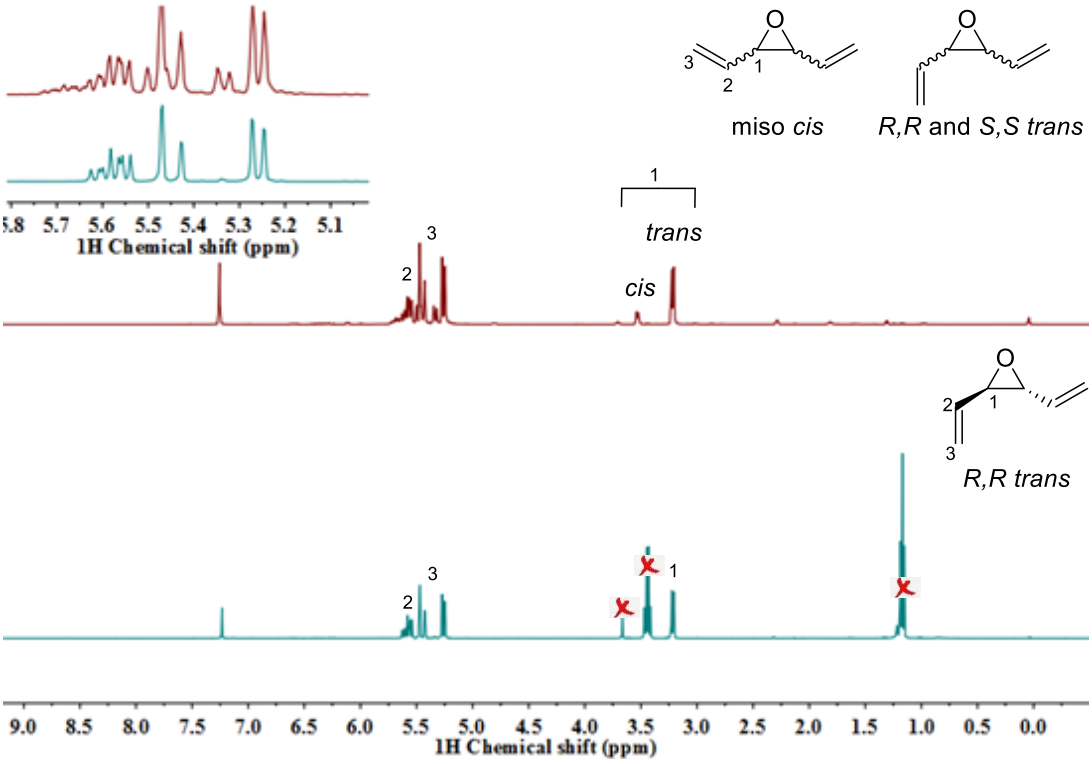


Figure 3.1 ^{1}H-NMR ($CDCl_3$, 400 MHz) of racemic divinyl oxirane (**3.18** - top) and enantiopure *R,R trans* divinyl oxirane (**3.11** - bottom).

3.4 ROP of divinyl oxirane

Ring-opening polymerisation of mono-substituted epoxides is well known and covered widely by Frey *et al.*[14] In sharp contrast, ROP reactions of 2,3-disubstituted oxiranes are limited and reported mainly for 2,3-dimethyloxirane,[15-17] and 1,2-epoxycyclohexane.[18-21] To the best of our knowledge, ROP of divinyl oxirane (**3.18**) has not been reported but since TPP(AlCl) was used for ROP of 2,3-dimethyloxirane[16,22] we thought that this catalyst would also be able to polymerise **3.18**. Conducting the polymerisation at room temperature and even at 60 °C did not yield more than 4% conversion after 10 days. However, adding 1 mol % of methylaluminum *bis*(2,4,6-tri-*tert*-butylphenolate) [MAlBP] as a bulky Lewis acid to the reaction led the polymerisation to reach 41% conversion determined from the crude ^{1}H-NMR spectra. The conversion was calculated using the relative integration of the peak attributed to the polymer **(3.24)** at 4.41-3.66 ppm and the peaks (*cis* and *trans*) attributed to the monomer **(3.18)** at 3.53 and 3.21 ppm. The polymer was purified by Sephadex column and the structure was confirmed by the NMR spectroscopy (^{1}H-

NMR and ^{13}C-NMR spectra, Figures 3.2 and 3.3). The molecular weight was analysed by GPC to give the expected M_n with relatively high dispersity (*Đ* 2.12).

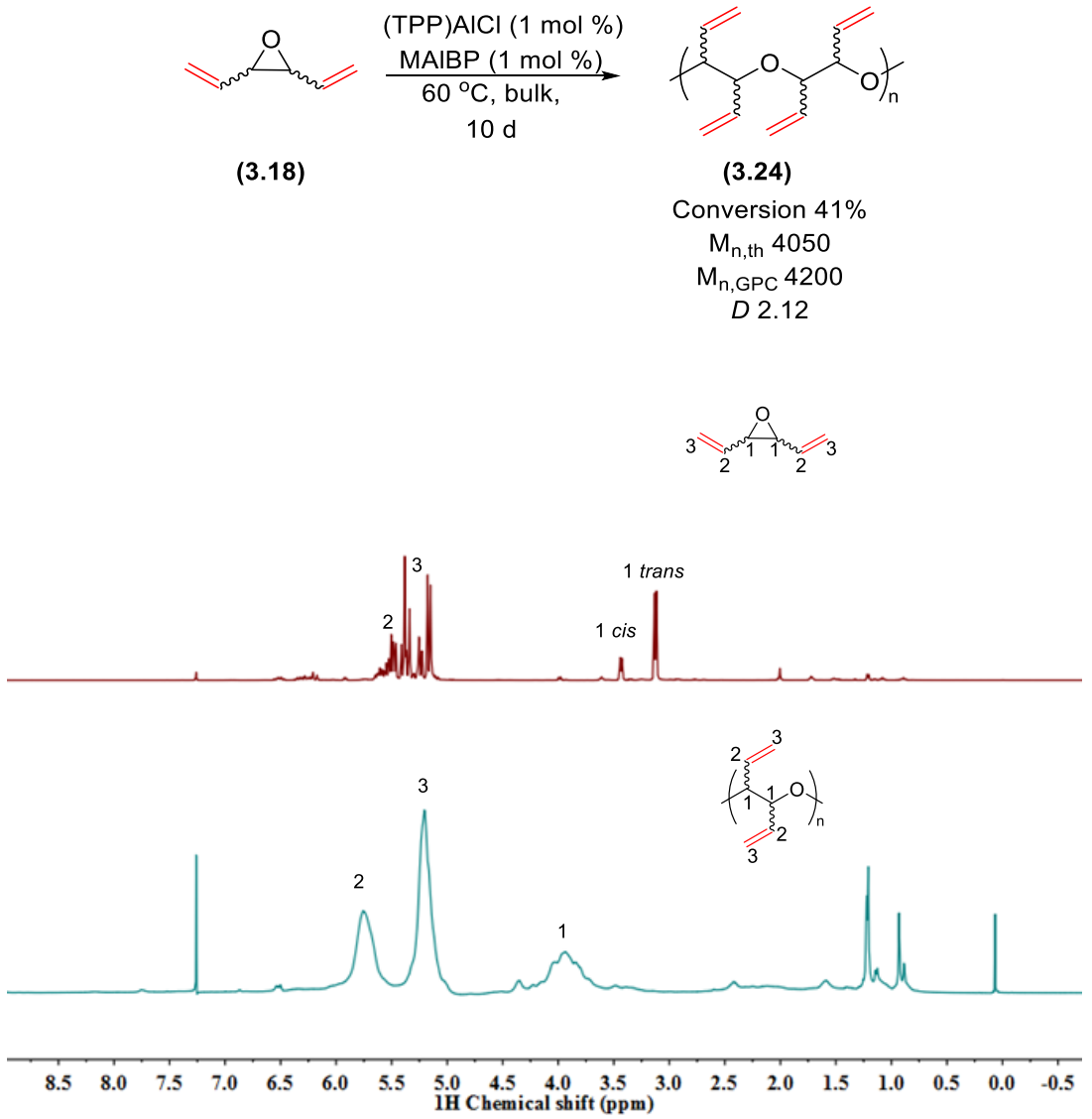


Figure 3.2 ^{1}H-NMR (*$CDCl_3$*, 400 MHz) of racemic divinyl oxirane (**3.18** - top) and atactic poly(divinyl oxirane) (**3.24** - bottom).

The broad peaks appearing in the ^{13}C-NMR reflect the atacticity of the polymer produced. Since the ^{13}C-NMR of the starting polymer is broad, RCM for this polymer will not provide any valuable information. For this reason, the future work of this chapter consists in optimising the synthesis of *trans*-divinyl oxirane (**3.18**) to afford it in a reasonable yield. Then, ROP of **3.18** should afford an isotactic polymer with single sharp carbon peaks.

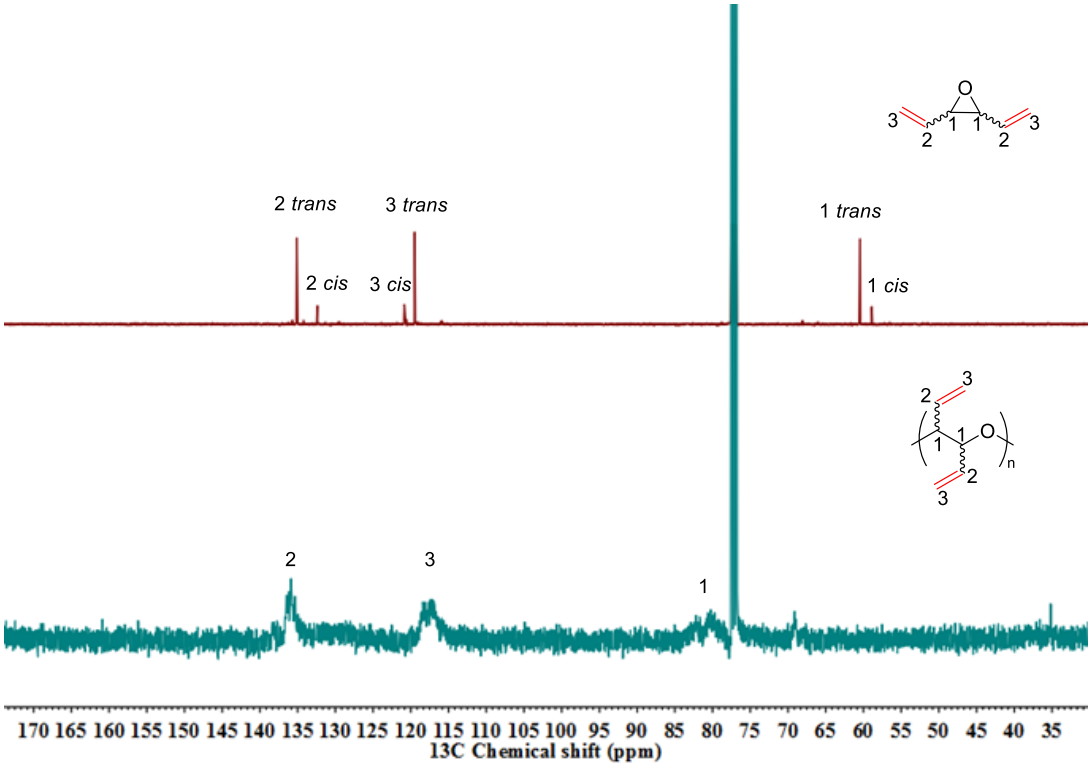


Figure 3.3 ^{13}C-NMR (*CDCl*$_3$, 100.2 MHz) of racemic divinyl oxirane (**3.18** - top) and atactic poly(divinyl oxirane) (**3.24** - bottom).

3.5 Conclusion

Although the ring-size selective RCM reaction was not investigated, this chapter derived a novel polymer of divinyl oxirane by ROP. Conducting the ROP at 60 °C did not cause isomerisation. However, the polymerisation rate was slow to afford around 40% monomer conversion after 10 days using (TPP)AlCl and MAlBP as an initiator and a monomer activator, respectively.

Also, a synthetic route to afford enantiopure divinyl oxirane was reported. However, the yield was relatively poor.

3.6 References

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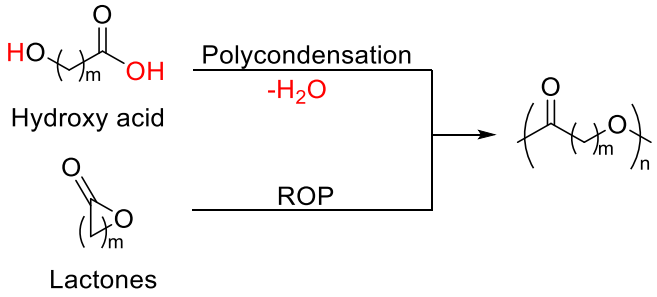
Chapter 4. A Step towards Functionalisable Cyclopolyesters

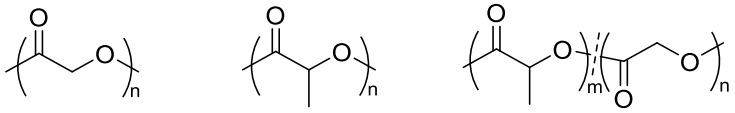
4.1 Polyesters

Polyesters are synthetic polymers where the individual units are held together by ester linkages. Polyesters are considered the most commercially competitive biocompatible, and biodegradable polymers for biomedical applications. They can be produced in a cost-effective way with a broad spectrum of characteristics. They are widely used as controlled drug delivery vehicles and for the manufacturing of different medical devices, such as fixation devices, plate, sutures, stent, bone, screws and tissue repairs.[1] In general, the starting units of aliphatic polyesters are either hydroxy acids or lactones (Scheme 4.1).



Scheme 4.1 The synthetic routes to aliphatic polyesters from starting monomers.

Hydroxy acids consist of a carboxylic acid substituted with a hydroxyl group separated by at least one carbon. The first carbon atom after the carbon in the -COOH group is labelled α, the second is labelled β, and so forth. In lactones, these prefixes also indicate the size of the lactone ring: α-lactone = 3-membered ring, β-lactone = 4-membered, γ-lactone = 5-membered, etc or named as propio, butyro, valero, capro, etc. Poly(α-hydroxy acids) such as poly(glycolic acid) (PGA) (**4.1**), poly(lactic acid) (PLA) (**4.2**), and poly(lactic-*co*-glycolic acid) (PLGA) copolymer (**4.3**) are the most commonly used biodegradable synthetic polymers in drug delivery and tissue engineering (Figure 4.1). The chemical properties of these polymers make them unique among many other PAHAs. PGA is a hydrophilic and highly crystalline polymer with a relatively fast degradation rate.[2,3]



PGA (4.1) PLA (4.2) PLGA (4.3)

Figure 4.1 The chemical structures of PGA, PLA and PLGA.

However, PLA exhibits different mechanical, physical and chemical properties due to the presence of a pendent methyl group on the alpha carbon. Generally, the copolymer PLGA is preferred compared with its constituent homopolymers for the fabrication of bone substitute constructs and many other biomedical purposes.[4] The degradation profile of PLGA can be controlled by varying the ratio between its monomers. PLA and PLGA exhibit high mechanical strength while having the ability to be shaped and moulded, which is ideal for a variety of applications in the polymer industry. Many applications of polymeric materials depend on the polymer's glass transition temperature (T_g).[5,6] This is often due to changes in the polymer's physical properties as it is heated through its glass transition temperature. These changes include but are not limited to increased permeability, loss of dimensional stability, and increased resilience.[7] The T_g of polymeric materials is dependent on the stereoregularity of the starting monomers.[8] Lactic acid, the monomer unit of PLA, exists as two enantiomers; L(+)- and D(-)- lactic acid (Figure 4.2). Since lactic acid has a stereogenic centre, PLA can be synthesised as its atactic, syndiotactic or isotactic form. From a thermoplastic application perspective, the T_g of isotactic PLA is relatively low at 50-60 °C.[9] However, for applications such as food packaging, resorbable sutures and surgical fixtures, this semi-crystalline PLA has near-ideal properties. In contrast, atactic PLA is an amorphous polymer and has a decreased T_g near room temperature.[10]

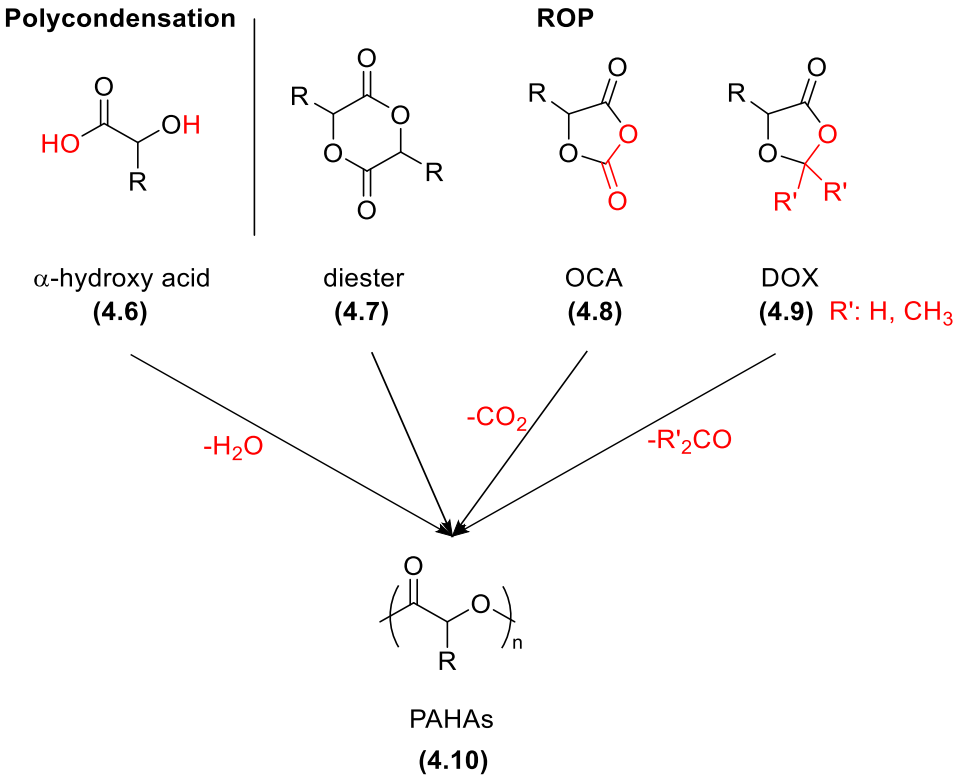
L(+)-lactic acid (4.4) D(-)-lactic acid (4.5)

Figure 4.2 The chemical structures of L- and D-lactic acid.

To improve the physical and chemical properties of polyesters many other substituted polyesters have been prepared from substituted α-hydroxy acid using a suitable polymerisation method.

4.2 Poly(α-hydroxy acids) synthesis

Polycondensation and ring-opening polymerisation (ROP) are the main routes for synthesising poly(α-hydroxy acids) (**4.10**).[11] Polycondensation involves the reaction of the hydroxyl and carboxylic acid entities of α-hydroxy acid (**4.6**) with a release of a water molecule. However, ROP involves the opening of lactones and their derivatives with or without releasing a small volatile molecule. These rings can be either diester (**4.7**), *O*-carboxy-anhydrides (OCA) (**4.8**) or 1,3-dioxolan-4-ones (DOX) (**4.9**) (Scheme 4.2).

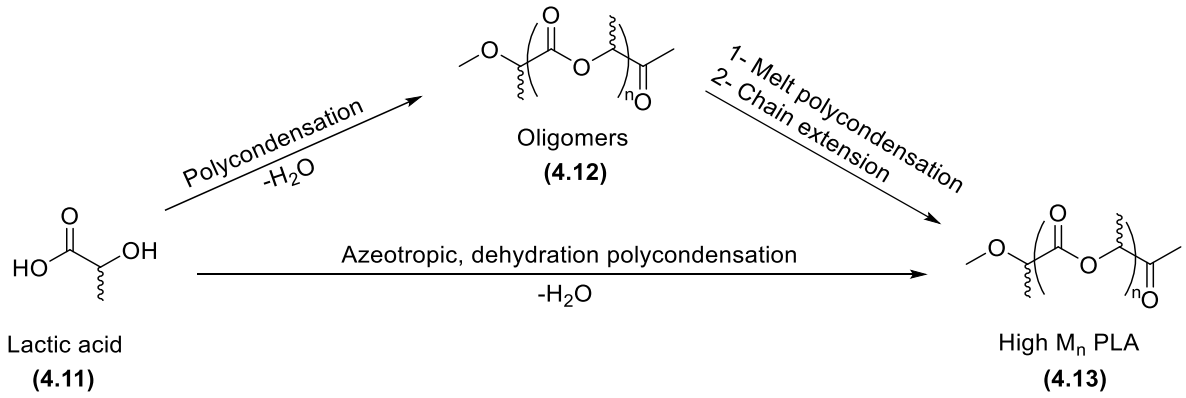


Scheme 4.2 The possible synthetic routes to PAHAs from four different starting monomers.

Besides these rings, α-lactones (3-membered ring) would be also a precursor for PAHAs but they have not been isolated in bulk due to their high reactivity.[12] The preparation and polymerisation of each of the above starting monomers has advantages and disadvantages.

4.2.1 Polycondensation

Polycondensation involves the reaction of the hydroxyl and carboxylic acid entities of α-hydroxy acid and is normally carried out in the melt. Removal of water formed during the condensation is critical to driving the reaction towards polymer formation. However, the high melt viscosity of the produced polymer inhibits the release of water from the melt.[13] To aid this, polymerisation is carried out under vacuum at high temperatures, but unwanted transesterification can lead to the formation of ring structures and broad dispersity. Transesterification is most prominent at temperatures >200 °C, thus reaction temperatures are kept below this but at the expense of a reduced reaction rate. Consequently, achieving high molecular weights of PLA, for example, with high mechanical strength is difficult by polycondensation. Similarly, polycondensation in a solution using azeotropic dehydration is another route to yield PLA with the added advantage of achieving higher molecular weight polymers with easier water removal (Scheme 4.3).[14]



Scheme 4.3 The synthetic route of high molecular weight of PLA by polycondensation.

However, extra labour-intensive steps are required, and the boiling point of the solvent restricts the reaction temperature.[14] For this reason, the industrially significant route to PLA synthesis uses ROP of lactones.

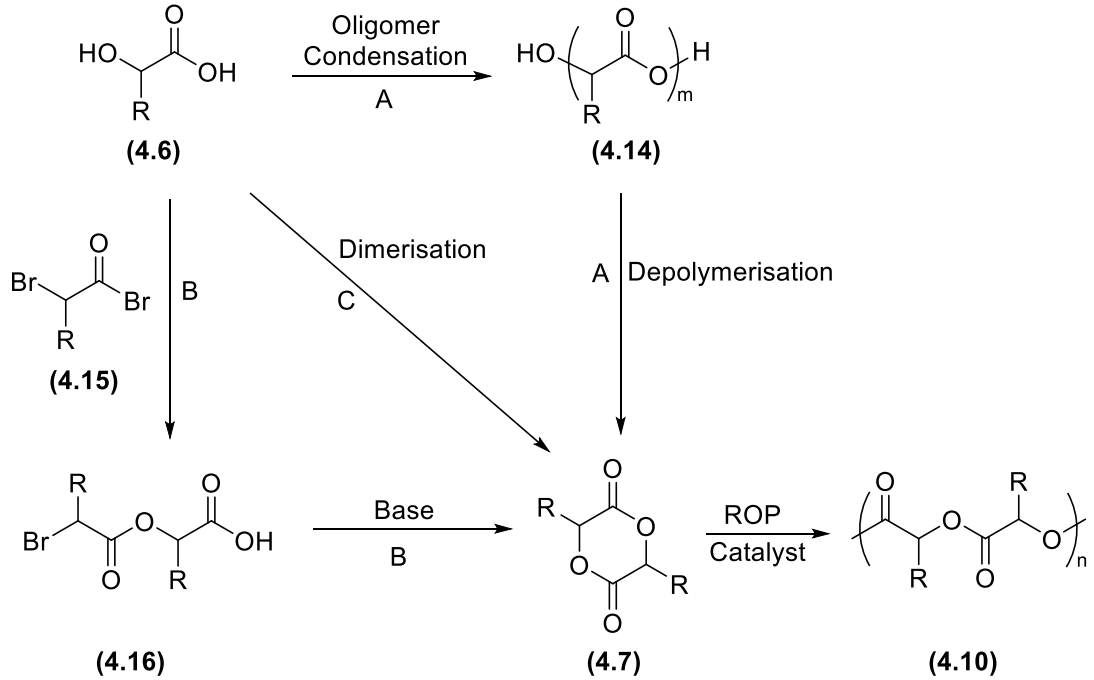
4.2.2 Ring-opening polymerisation (ROP)

As a synthetic strategy, ring-opening polymerisation differs greatly from polycondensation. The greatest difference derives from the contrast between step-growth and chain-growth polymerisations. ROP is a chain growth process which progresses *via* initiation, then propagation and finally termination. Initiation occurs

generating a reactive species. It combines with a monomer to produce a molecule with a reactive chain end. This species takes part in propagation, reacting with monomers and elongating the reactive species. The polymer chain grows without termination until the introduction of an external quenching or termination source to the system. The molecular weight or the degree of polymerisation of the growing chain is aligned with the ratio of the monomer to the initiator.[15] Thus, ROP of cyclic-ester monomers has several advantages over polycondensation. However, synthesising cyclic-ester monomers from hydroxy acids need an extra synthesis step and challenging work. Up to date, three classes of cyclic-esters monomers have been being synthesised and used for preparing high molecular weights and controlled structure of PAHAs.

4.2.2.1 Lactones

Lactones, (**4.7**) are the common cyclic monomers for synthesising PAHAs. They have proven a useful route to access not only lactide but also a wide variety of substituted cyclic monomers. In 1999, Baker *et al.* reported three synthetic pathways to form substituted cyclic-diesters (Scheme 4.4).



Scheme 4.4 Synthetic routes to functionalised derivatives of lactide starting from α-hydroxy acids. Route a) oligomer condensation. Route b) condensation of α-hydroxy acids and α-bromoacyl bromides. Route c) dimerisation.

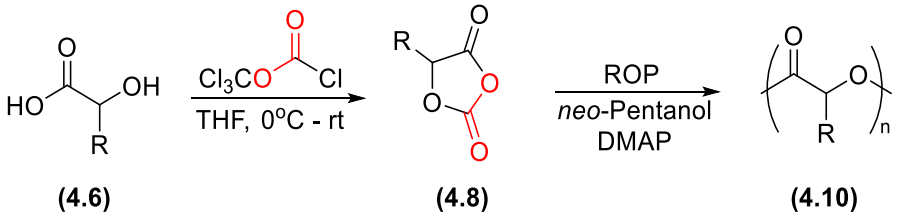
Route A is analogous to the formation of lactide; oligomer (**4.14**) formation *via* condensation of two substituted α-hydroxy acids followed by cracking under reduced pressure in the presence of a transesterification catalyst. Route B offers more flexibility for creating unsymmetrical dimers (**4.16**), where an ester is formed from the condensation of an α-hydroxy acid with an α-bromoacyl bromide (**4.15**) followed by ring closure to yield the cyclic dimer. Route C is the direct acid catalysed dimerisation of two α-hydroxy acids.[16]

The chain growth of cyclic diesters polymerisation is driven by the relief of ring strain. The ring strain relieved upon the opening of a cyclic-diester is not usually associated with six-membered rings, but it is derived from the two sp^2 hybridised ester moieties. These two planar conformations within the ring lead to its strained skew boat conformation.[17] ROP goes by a pseudo-anionic mechanism in the presence of a catalyst. This provides control over the polymerisation and does not require the stringent conditions required for other mechanisms.[18] However, the relief of ring strain, which provides the driving force for the ROP, remains modest so that highly active promoters are required if the ROP of lactide is to proceed under mild conditions.[19] In order to overcome these limitations, activated equivalents of lactide would be highly desirable. However, this is associated with significant amounts of undesirable transesterification reactions.[20,21] Moreover, the synthesis of the required diester monomers is often challenging and low yielding after complex separations, especially for preparing substituted diesters. The high temperatures used during synthesis often results in a mixture of diastereomers, which in turn inhibits the access to isotactic PAHAs. Also, the substituted diesters display poor reactivity which leads to long polymerisation times and the need for elevated temperatures.[22-27] For these reasons, polymer chemists have been trying to find alternative routes to PAHAs.

4.2.2.2 *O*-carboxy-anhydride (OCA)

Bourissou and coworkers devised an alternate route by ring-opening polymerisation of *O*-carboxy-anhydrides (OCAs), which is driven by the release of CO_2 (Scheme 4.5). OCAs (**4.8**) are typically prepared via carbonylation of α-hydroxy acids. Phosgene, diphosgene and triphosgene are typically used as carbonylating agents.[28] Despite diphosgene and triphosgene requiring activated charcoal and stoichiometric *tert*-amines, they are often preferred over phosgene due to their lower volatility making

them easier to handle. OCAs have provided an extremely useful synthetic route to PAHAs. While boosting the monomer's activity in polymerisations, the monomers were also frequently obtained in higher yields than their diester counterparts. The higher activity has led to the use of ambient temperatures which has likely played a large factor in the increased control over polymerisations. The simplicity of OCA synthesis and its high yields have been beneficial in synthesising polymers unique to those synthesised from cyclic diesters.[29-32]



(4.6) (4.8) (4.10)

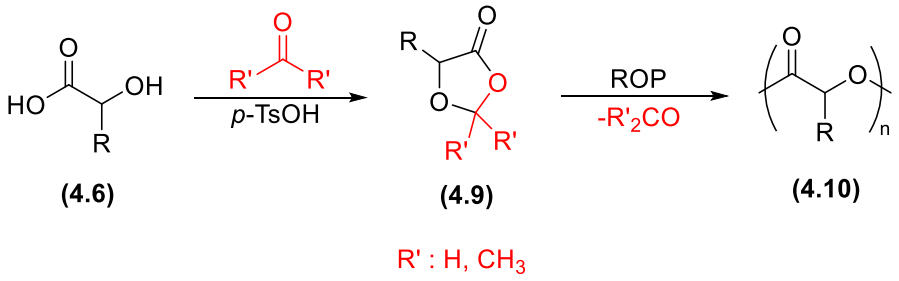
Scheme 4.5 Carbonylation of α-hydroxy acid to afford *O*-carboxy-anhydride cycle which can be polymerised to afford PAHAs.

However, there are several drawbacks to using OCAs as a monomer source. Firstly, the cost of monomer synthesis is increased dramatically. This is due to the price of triphosgene being far greater than the α-hydroxy acid; for example, the price of 500 g of triphosgene is 20 times higher than that of 1 L of lactic acid (80%) (prices from Sigma Aldrich May 2019). The health and safety of the users are put at far greater risk when synthesising OCA monomers.[33-35]

4.2.2.3 1,3-dioxolan-4-ones (DOX)

Due to the obstacles of preparing lactones and OCAs monomers, the Shaver group recently developed a new synthetic methodology that would access the same broad functional group tolerance, but derive from sustainable, scalable and inexpensive resources. They reported ring-opening polymerisation of renewable substituted 1,3-dioxolan-4-ones (DOX) (**4.9**), eliminating formaldehyde or ketones to afford structurally diverse PAHAs (Scheme 4.6).[36,37] The use of 1,3-dioxolan-4-ones as monomers to form polymers was first patented 23 years ago. Hermes stated that "useful polymeric material" was obtained from the homopolymerisation of (**4.17**).[38] Later, Miller patented a less ambiguous invention of the polymerisation of (**4.17**) as a monomer feedstock. The patent specifies that the polymerisation of produces a polymer and its repeat unit retains the acetal present in the monomer.[39,40] However,

the ^{13}C-NMR spectrum did not display the acetal peak and it has been concluded by the Shaver group, using the same polymerisation protocols, that the polymer produced is a polyester and not a polyesteracetal.



Scheme 4.6 1,3-dioxolan-4-ones formation from α-hydroxy acid which can be polymerised to PAHAs.

The Shaver group found that (**4.17**) can be copolymerised with (L-lactide) to make a copolymer of PAHAs.[36] However, ROP of (**4.17**) to form a homopolymer was inconclusive. In order to synthesise homopolymers from 1,3-dioxolan-4-ones, further substitution on the ring was necessary. The scope of (**4.17**) was expanded to include phenyl, methyl, *iso*-propyl, cyclohexyl, n-butyl, and *iso*-butyl substituents at the five position. Substituted DOX monomers (**4.18** - **4.22**) (Figure 4.3) were homopolymerised and led to the formation of the desired PAHAs with paraformaldehyde as a polymerisation by-product.[36] Also, the polymers were prepared with high retention of stereochemistry, meaning isotactic polymers are easily prepared from natural enantiopure feedstocks.

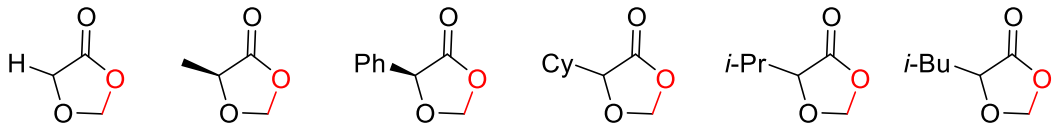


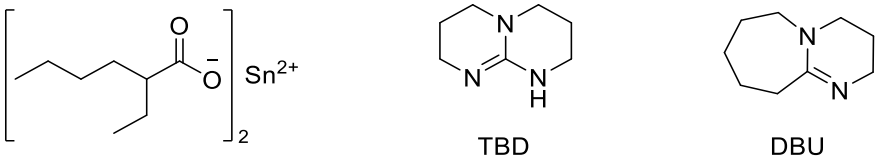
Figure 4.3 A selection of DOX monomers prepared by the Shaver group from α-hydroxy acid derivatives.

The yields of formation of polymers using the 1,3-dioxolan-4-one monomers were all improved upon the yields using their diester counterparts. Other advantages of using DOX monomers compared to the previously discussed monomers is the higher polymerisation conversion. Five-membered lactones have been shown to have less

ring strain than the six-membered ring strain, and thus, it is the elimination of formaldehyde that promotes the ROP of DOX monomers.

4.3 Ring-opening polymerisation of lactones

Metals have been central to the catalytic systems employed for the ROP of cyclic esters. The most widely used catalyst in the industry is tin(II) 2-ethylhexanoate or tin octanoate (**4.23**). It remains the first-choice catalyst for polymerising cyclic esters due to multiple factors: the ease with which it can be handled, its aliphatic ligand framework exhibiting good solubility in most common organic solvents or bulk monomer, and its high activity with typical reaction times ranging from minutes to hours rather than hours to days in polycondensation. However, this catalyst promotes transesterification, a side reaction which leads to broad dispersities (*Đ*s).[41] The increase in *Đ* is caused by the active polymer chain end reacting with either another chain or undergoing backbiting. Not only metal catalysts are used for this purpose; organocatalysts such as triazabicyclodecene (TBD - **4.24**) and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU - **4.25**) are also used in the ROP of lactide but these type of catalysts also promote transesterification and broad (*Đ*s).[42] Although the three previous catalysts facilitate ROP of lactide monomers, they are poor catalysts for the ROP of DOX monomers.[43]



(4.23) TBD (4.24) DBU (4.25)

Figure 4.4 The chemical structures of tin octanoate, TBD and DBU.

On the other hand, a range of metal alkoxides has been reported for ROP of lactide and DOX monomers with retention of configuration to yield isotactic or atactic polymers with narrow *Đ*s.[44,45] One of the most explored complexes for stereocontrolled polymerisation of lactide are the aluminium salen species (Al-Salen). Spassky found that using *N,N′*-bis(salicylidene)-1,2-ethanediamine (salen) ligated aluminium alkoxide species helped to control the polymerisation displaying living characteristics.[46] The reactivity of these catalysts was modified mainly by varying the

diamine bridges, and the ligand's phenoxide substituents (R). A selection of the most common used Al-Salen catalysts is in Figure 4.5. Each variation has an advantage and disadvantage in terms of yield, polymerisation rate, dispersity, control tacticity and stereoselectivity, and reactivity at different temperatures.[43]

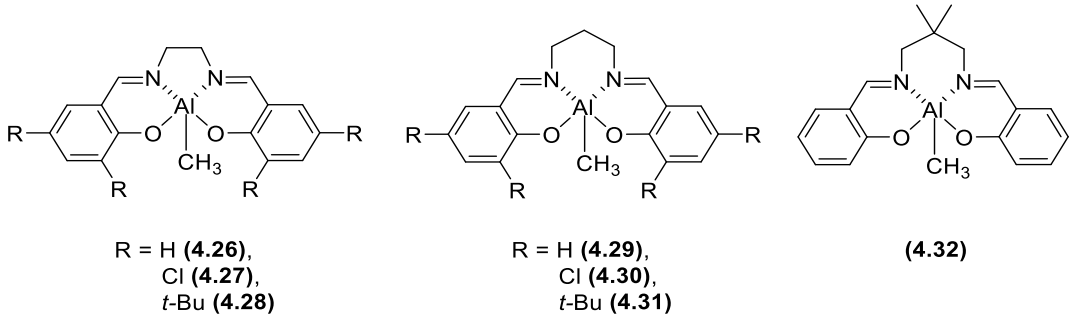
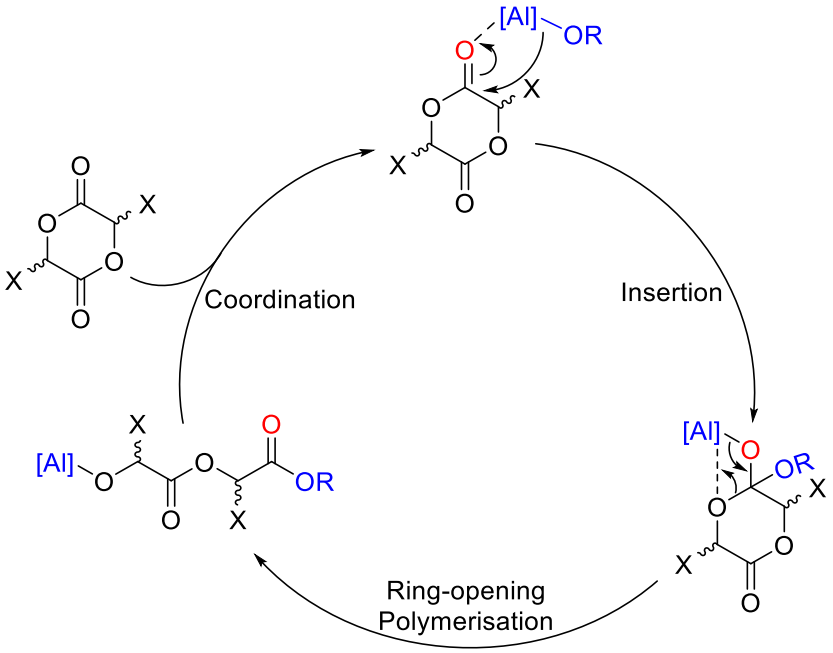


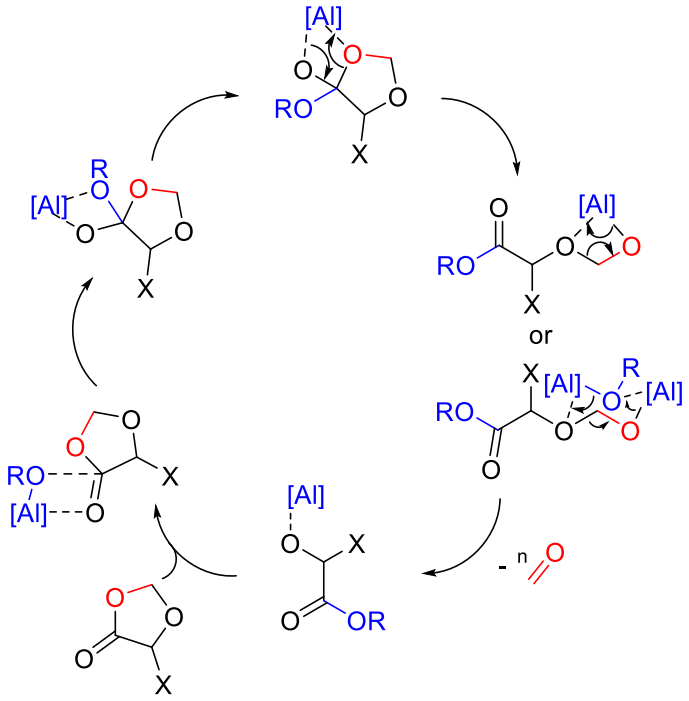
Figure 4.5 A selection of the most common Al-Salen catalysts.

The mechanism for aluminium-mediated ROP of lactide monomers has been well studied with the first hypothesis of the coordination-insertion mechanism developed by Dittrich and Schulz.[47] The mechanism has been shown to follow a route consisting of initiation, propagation and termination (Scheme 4.7). Initiation and propagation: aluminium coordinates to the oxygen of the carbonyl and promotes the alkoxide's insertion into the carbonyl.



Scheme 4.7 Coordination insertion mechanism for the ROP of cyclic-diester by alkoxide Al-Salen catalyst.

Whilst bound to the monomer, aluminium coordination to the acyl oxygen promotes the reformation of the carbonyl and leads to acyl bond cleavage. Termination occurs upon the addition of exogenous alcohol, leading to alkoxide exchange between the polymer chain end and alcohol (Scheme 4.7). However, the catalytic mechanism of ROP of DOX monomers is different due to the presence of formaldehyde in the catalytic cycle (Scheme 4.8).[37] The presence of formaldehyde in the monomer gives an appropriate amount of ring-strain which leads its release in the ring-opening elimination polymerisation. Back-biting of the chain after cleavage of the ester acyl bond facilitates this release, either by a 4-membered metallacycle form, or by a bimetallic mechanism which could promote formaldehyde release *via* a 6-membered intermediate.



Scheme 4.8 Coordination-insertion mechanism of the polymerisation of 1,3-dioxolan-4-ones.[37]

Expulsion of formaldehyde is visible as the reaction proceeds, forming as a white solid at the top of the reaction vessel. Cairns *et al.* found that (**4.29**) and (**4.30**) catalysts showed the best ROP results of DOX monomers in terms of the yield, polymerisation rate, dispersity and tacticity control.[43]

4.4 Post-polymerisation modification of PAHAs

Although PLA has an established commercial prevalence, it has limitations. This includes low thermal resistance, poor toughness, brittleness, poor gas barrier properties and no possible functionalisation. These drawbacks make PLA processing difficult and narrow the end application scope. Moreover, for more advanced medical and pharmaceutical applications, polyesters are being modified to solve issues such as hydrophobicity, low cell adhesion, and inflammatory side-effects.[1] The lack of functional handles on lactide coupled with its reactive esters limit modification without losing the ring structure. Incorporating functionalities along the polymer chain has been used to obtain the desired structures and property tuning capability. Many substituted monomers have been made for preparing tuneable poly(α-hydroxy acid)s with a wide range of functional groups (Figure 4.6). The main aim of synthesising substituted PAHAs is expanding the applications of these biodegradable materials by improving their chemical and physical properties, especially T_g.

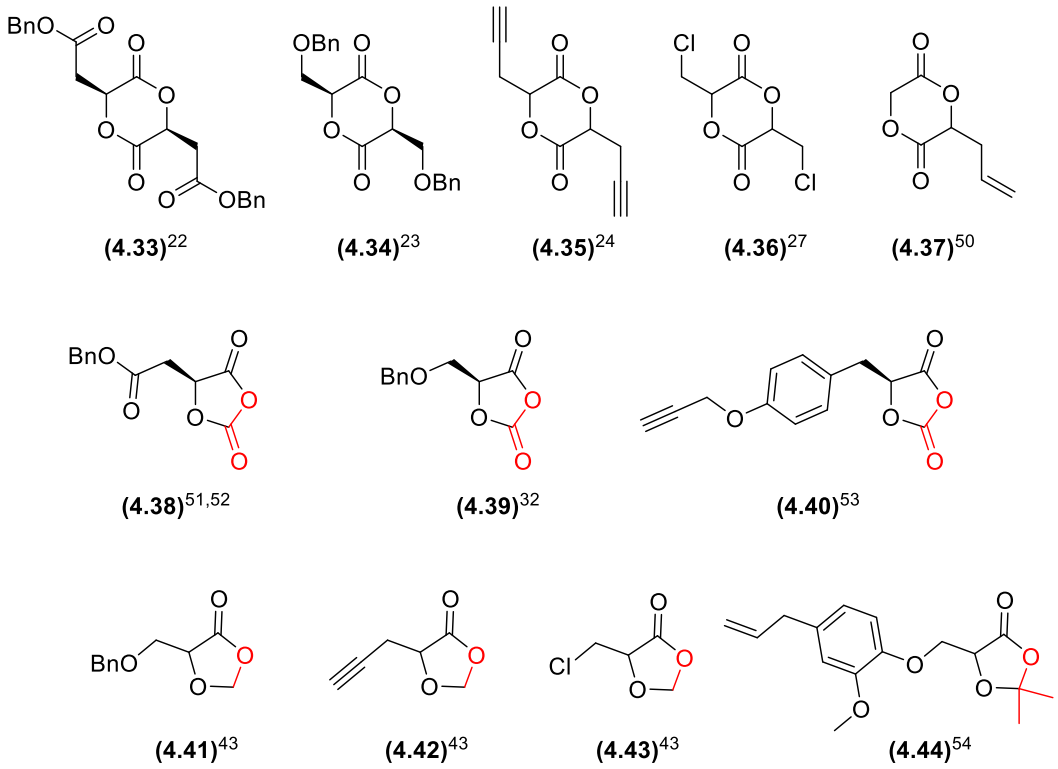


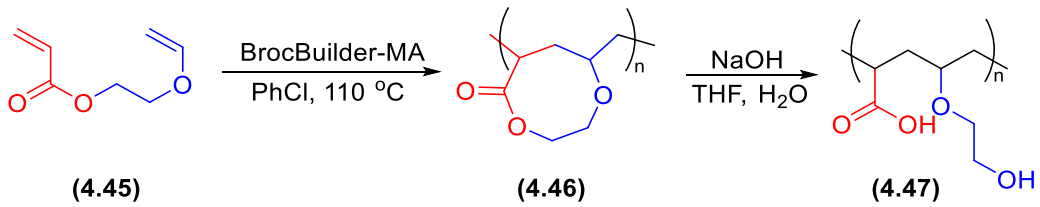
Figure 4.6 A selection of functionalised cyclic ester monomers.

The alkyl- and aryl-substituted PAHAs' properties have been tested for use in biomedical applications; however, these substituents offer low solubilities and limited

interactions with biomedical agents and thus reducing their versatility.[48,49] More functionalities other than the alkyl and aryl side chains have been researched with the aim of attaining the desired properties. However, when the desired functional groups, such as hydroxyl or carboxyl, would inhibit or affect the polymerisation then these groups were obtained by either protected substituted monomers or by post-polymerisation modification of a pre-made polymer. However, the chemical functionalisation of polyesters is not the only way to improve the properties of the polyester and expand its application. Changing the topology of a polyester from a linear to other conformation also impacts on the physical properties, as mentioned in chapter one.[55]

4.5 Cyclopolyester

To the best of our knowledge, no cyclopolyester has been reported in the literature yet. However, ester moieties (lactones) in the cyclic unit of cyclopolymers have been obtained by cyclopolymerisation of several divinyl and bis(diazoacetate) monomers.[56] Although these polymers are considered not biodegradable, since the linkages between the cyclic monomer units are C-C bonds, having an ester unit in these cyclo-structures would make these cyclopolymers suitable for post-polymerisation modification. Ouchi *et al.* reported on the cyclopolymerisation of acrylate-vinyl ether moieties (**4.45**) by BrocBuilder-MA, (*N*-(2-methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*O*-(2-carboxyprop-2 yl)hydroxyl- amine), where two different vinyl groups, acrylate and vinyl ether, are linked *via* an ester bond as the tethering moiety (Scheme 4.9).[57] The polymerisation was controlled to give polymers, with narrow dispersity.

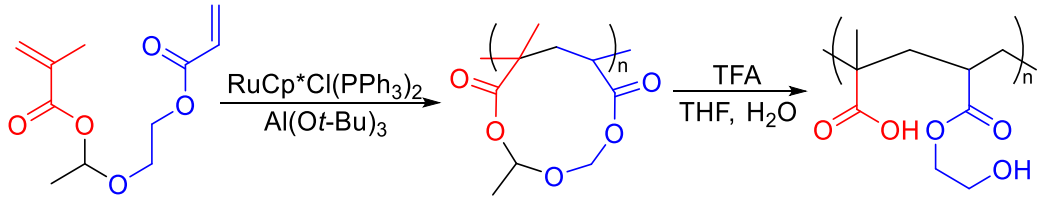


Scheme 4.9 Cyclopolymerisation of divinyl monomer, then hydrolysis to afford alternating copolymer of carboxylic and hydroxyl groups.[57]

The lactone bonds were cleaved to convert into the essentially alternating copolymer of carboxylic and hydroxyl groups (**4.47**), which exhibited a higher glass transition

temperature than that estimated from the composition ratio and T_g values of the homopolymers. While the T_g of poly(acrylic acid), and poly(2-hydroxyethyl vinyl ether) homopolymers are 117.0 °C and 10.2 °C, respectively, the T_g of the copolymer after ester cleavage (**4.47**) is 91.7 °C.

In another example, the alternating sequence of -COOH and -OH pendents specifically provided a lower critical solution temperature (LCST) in an ether solvent, which was not observed with the random copolymer of same composition ratio (Scheme 4.10).[58]

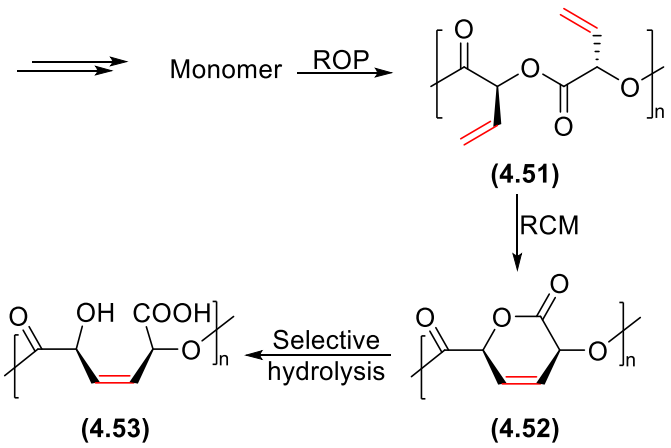


(4.48) **(4.49)** **(4.50)**

Scheme 4.10 Cyclopolymerisation of **4.48** with a cleavable hemiacetal ester bond reported by Ouchi *et al.*[58]

4.6 Aims and objectives

Although olefin cross metathesis was used for post-polymerisation modification of polyesters, olefin cross- or ring-closing metathesis of olefin substituted PAHAs had not been reported before the date of this work. The aim of this chapter is to prepare olefin substituted poly(α-hydroxy-acid) as a starting platform suitable for ring-closing metathesis to afford a biodegradable cyclopolyester. The distance between the olefin pendent group in poly(vinyl glycolic acid) (PVGA - **4.51**) would be ideal for RCM to obtain six-membered ring of functionalisable cyclopolyesters (**4.52**). However, since there is no commercially available starting monomer for PVGA, monomer synthesis is needed. A selection of catalysts will be examined to achieve a controlled polymerisation of the synthesised monomer. Then, PVGA will be treated with metathesis catalysts to investigate the possibility of obtaining cyclopolyester by ring-closing metathesis (RCM) (Scheme 4.11).



Scheme 4.11 A proposed synthetic route to functionalisable cyclopolyesters by RCM.

RCM of PVGA would produce the first biodegradable cyclopolyester. This unique cyclostructure would have a significant impact on the thermal properties of the produced cyclopolyester since this polymer would tend to be planar due to the conjugation between the ester, lactone and alkene groups along the polymer backbone. The internal olefin would also be functionalisable to produce a wide range of functionalised cyclopolyesters. Also, selective hydrolysis of the lactone would afford an alternating sequence of -COOH and -OH pendents of an unsaturated polyester backbone with exclusively *Z* olefins (**4.53**) as potentially water-soluble polyester with relatively high glass transition temperature.

4.7 Monomer synthesis towards PVGA

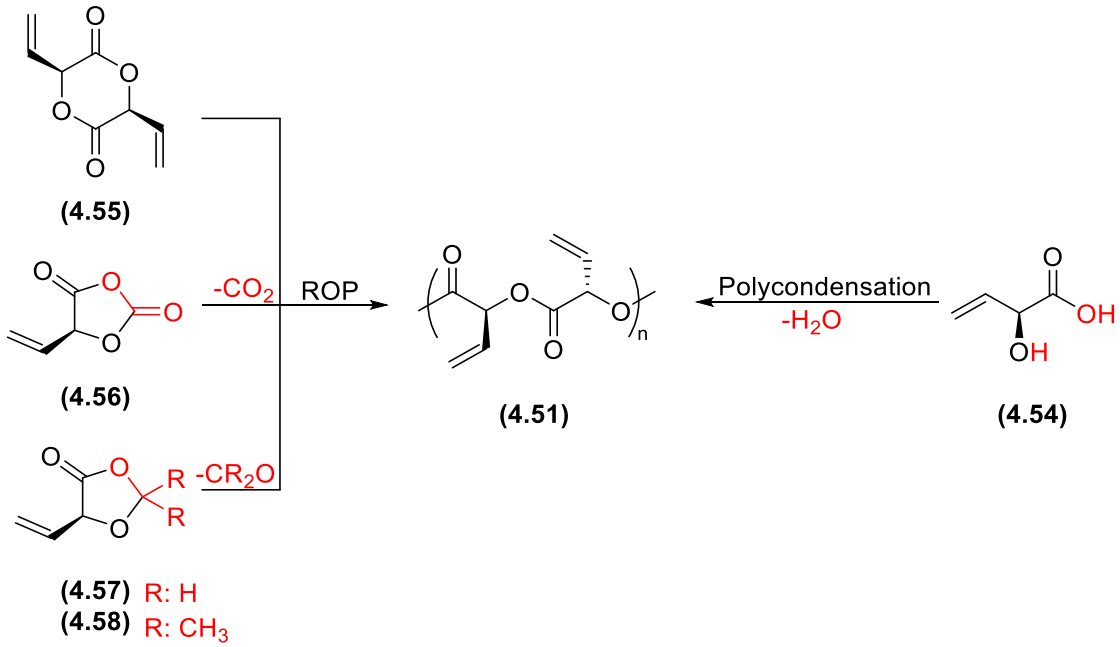
PVGA can be prepared by either polycondensation of enantiopure (*S*)-vinyl glycolic acid (**4.54**) or by ROP of either;

1- (*3S,6S*)-Vinylglycolide dimer (**4.55**) or

2- (*5S*)-vinyl-1,3-dioxolane-2,4-dione (*S*-vinyl-OCA - **4.56**) by the release of CO_2 or

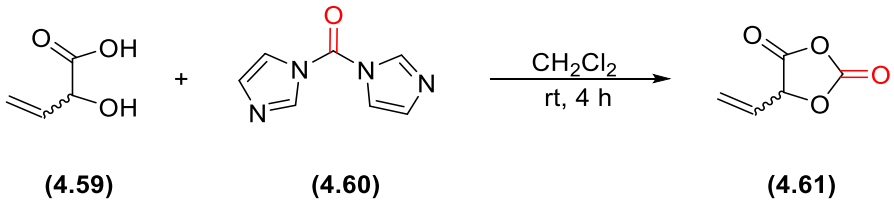
3- (*5S*)-vinyl-1,3-dioxolan-4-ones (*S*-vinyl-DOX - **4.57**) or (5*R*)-vinyl-dimethyl-DOX (**4.58**) by the release of formaldehyde or acetone, respectively (Scheme 4.12).

Due to the disadvantages of α-hydroxy acid polycondensation, ROP of cyclic esters towards PVGA was our focus. Also, although enantiopure monomers were sought to afford stereocontrolled polymers, we were working toward synthesising the required monomer regardless of its enantiomeric purity.



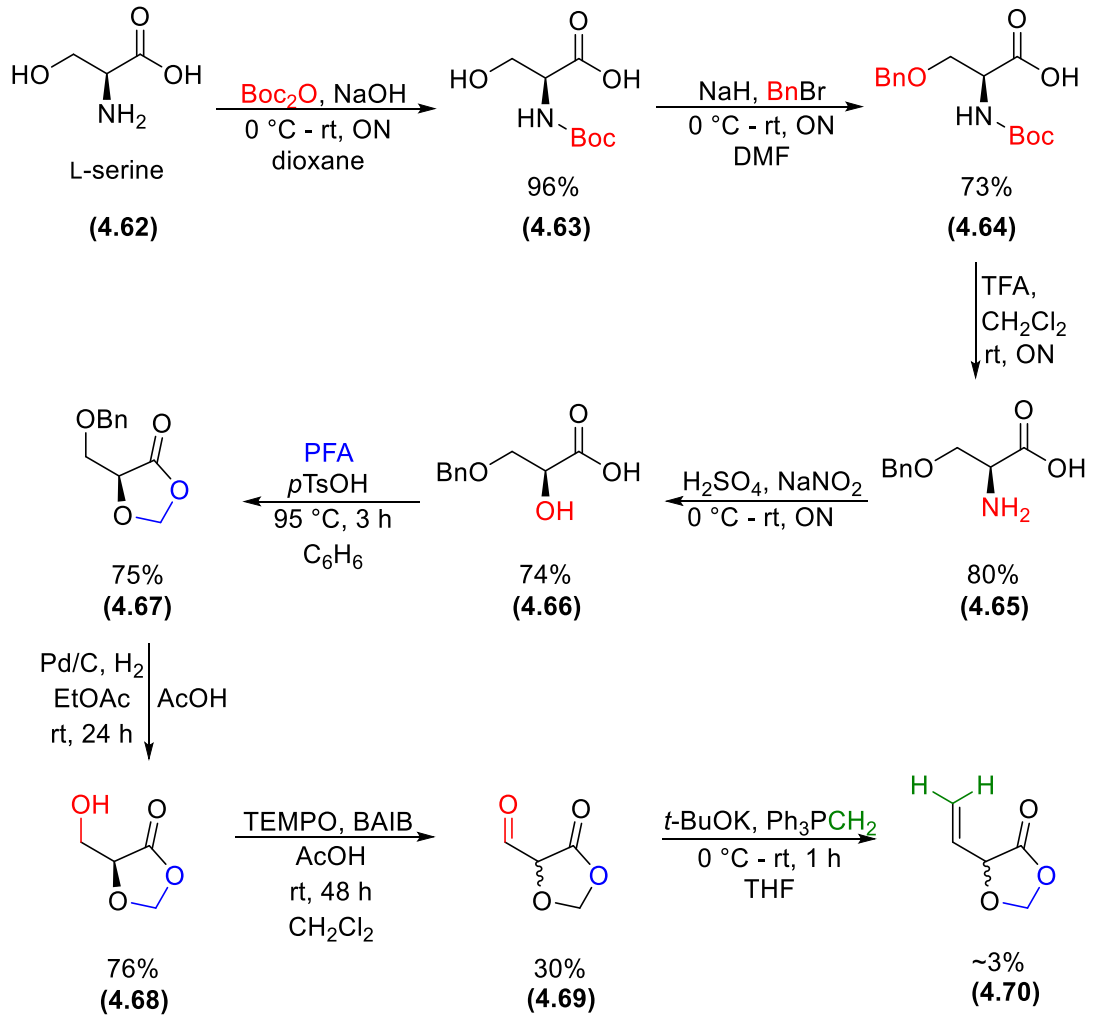
Scheme 4.12 Possible synthetic routes towards isotactic PVGA.

A homopolymer of PVGA had not been reported in the literature yet. However, a copolymer of (PVGA-PLA) was synthesised once by Sels *et al.* using ROP of racemic vinylglycolide dimer with lactide. Vinylglycolide dimer was made by the Sels group from *rac*-vinyl glycolic acid in *o*-xylene or toluene using a zeolite-based catalytic process to afford only 16 - 24 % yield of the cyclic dimer.[59] The low yield they obtained encouraged us to turn our attention to prepare PVGA from either vinyl-OCA (**4.56**) or vinyl-DOX (**4.57** and/or **4.58**). Vinyl-OCA (**4.56**) could be prepared by carbonylation of enantiopure (*S*)-vinyl glycolic acid. However, using an expensive and toxic gas of triphosgene as a carbonylation agent was not favoured. Blanchard *et al.* patented in 2010 a synthetic route to substituted OCA monomers using 1,1'-carbonyldiimidazole (**4.60**) as a carbonylation agent. They synthesised dimethyl-OCA with ~80% yield by carbonylation of dimethyl glycolic acid using **4.60**.[60]



Scheme 4.13 A synthetic route of vinyl-OCA using 1,1'-carbonyldiimidazole as a carbonylation agent.

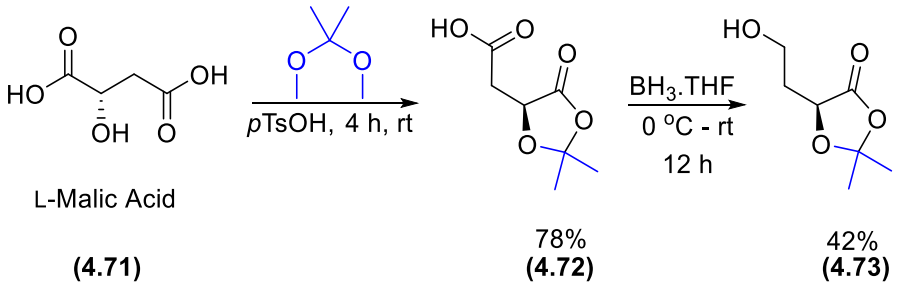
However, when we used the reaction conditions on racemic vinyl glycolic (**4.59**) acid many side products were obtained along with only 15% of vinyl-OCA (**4.61**) (Scheme 4.13). Also, the isolation and purification were challenging. For this reason, we moved toward preparing vinyl-DOX. Several attempts were tried to synthesise an enantiopure vinyl-DOX as a precursor for an isotactic starting polymer. The initial attempt started from an inexpensive amino acid, L-serine (**4.62**). The target synthetic route is summarised in (Scheme 4.14). The functionalities of amino acids have been utilised into lactone monomers synthesis, and their side-chains used as pendent groups of polyesters' precursors.[61] The chosen synthetic route was inspired by other work that has used amino acids starting materials in monomer and polyester synthesis.[43,61] The objective was to utilise L-serine to prepare substituted α-hydroxy acid which can be used for DOX ring formation.



Scheme 4.14 A synthetic route of vinyl-DOX from L-serine.

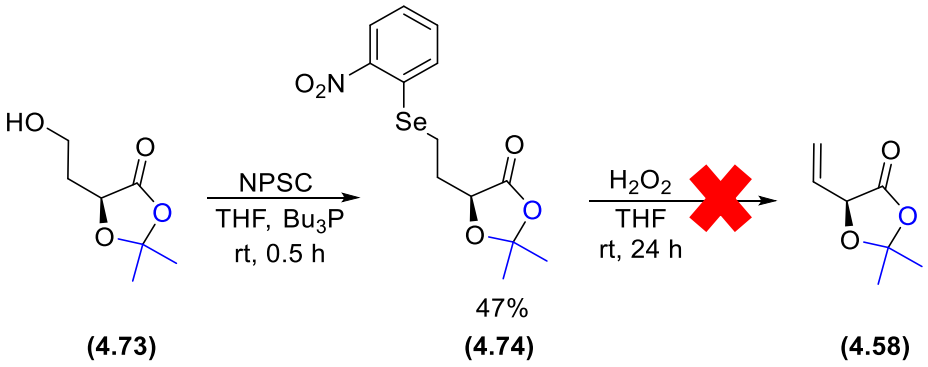
First, the amine protection of L-serine by a *tert*-butoxycarbonyl (Boc) protecting group was necessary to block the amine group and prevent its reaction with benzyl bromide (BnBr) in the hydroxyl protection step. Protection of the hydroxyl group was required in order to prevent side reactions such as dehydration. The benzyl protecting group was chosen due to its stability to trifluoroacetic acid (TFA) which was used in the Boc deprotection step. Then, the diazotization of the amine of (**4.65**) gave the α–hydroxy acid derivative as a precursor for DOX-ring formation. Benzyloxymethyl-DOX (**4.67**) was obtained following procedures previously reported by Cairns *et al.* by refluxing α–hydroxy acid (**4.66**) with an excess of paraformaldehyde (PFA) in the presence of para-toluenesulfonic acid (pTsOH) as an acidic catalyst.[36] A Dean-Stark apparatus was used to actively remove water. Cairns *et al.* used a large volume of a highly toxic solvent, benzene, for DOX monomer synthesis (50 mL for 7.5 mmol of α-hydroxy acid).[36] Using a smaller volume of solvent for this reaction would lead to a large number of side products. To overcome this issue, **4.66** (71 mmol) was added dropwise into the refluxed PFA and pTsOH suspension in a relatively small volume of benzene (100 mL) to give 75 % yield. To synthesise vinyl-DOX from benzyloxymethyl-DOX a further three-step reaction was followed. Deprotection of the benzyl group was performed using palladium-catalysed hydrogenation in the presence of acetic acid as a catalyst delivering hydroxymethyl-DOX (**4.68**). All the previous synthesis steps conserved the configuration of the molecule and gave relatively good yields. However, the oxidation of this primary hydroxyl, by 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) and bis(acetoxy)iodobenzene (BAIB), yielded 30 % only of the aldehyde derivative (**4.69**). Also, the configuration of the ring was not sustained due to the aldehyde-enol tautomerism. Moreover, Wittig reaction of this aldehyde gave traces of the desired product. For this reason, a more efficient and shorter synthetic route for making enantiopure vinyl-DOX was targeted. Here, the objective was to utilise DOX ring formation from an enantiopure (*5S*)-hydroxyethyl-dimethyl-DOX (**4.73**) as a precursor of (*5S*)-vinyl-dimethyl-DOX (**4.58**). Vinyl-dimethyl-DOX (**4.58**) can also be used as a monomer of PVGA, but ROP of dimethyl-DOX needs harsher conditions than ROP of DOX monomers to release acetone during the polymerisation.[43] Hydroxyethyl-dimethyl-DOX (**4.73**) has been reported by Denmark *et al.*[62] starting from a cheap enantiopure natural compound, L-Malic acid, which has been used to

synthesise polyester precursors.[63] L-Malic acid (**4.71**) was dissolved in excess 2,2-dimethoxypropane and the product was formed after 4 h of stirring at room temperature. The carboxylic group of the product (**4.72**) was reduced to hydroxyl using borane tetrahydrofuran complex (BH_3.THF) (Scheme 4.15).[62]



Scheme 4.15 A two-step reaction to prepare hydroxyethyl-dimethyl-DOX (**4.73**) from L-malic acid.

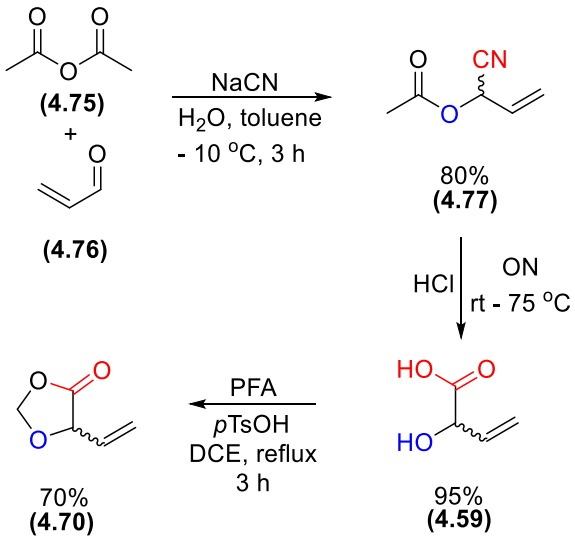
Then, an elimination reaction of hydroxyethyl-dimethyl-DOX (**4.73**) would lead to enantiopure vinyl-dimethyl-DOX. The Grieco elimination is a mild reaction for forming terminal alkenes from aliphatic primary alcohol.[64] The alcohol first reacts with *o*-nitrophenyl selenocyanate (NPSC) and *tri*-butylphosphine (Bu_3P) to form a selenide *via* a nucleophilic substitution on the electron-deficient selenium. In the second step, the selenide is oxidised with hydrogen peroxide to give a selenoxide. This structure decomposes to form an alkene by an E_i elimination mechanism (Scheme 4.16)



Scheme 4.16 A proposed reaction to prepare vinyl-dimethyl-DOX (**4.58**) from (**4.73**).

o-Nitrophenyl selenocyanate ethyl-dimethyl-DOX (**4.74**) was successfully obtained. This compound was then treated with hydrogen peroxide and the reaction was monitored by TLC. After 48 hours the reaction was judged to have reached completion as no starting material was left. However, quenching the reaction by sodium hydroxide decomposed the product as it was not noticed by the TLC after the work-up.

It has been noticed from this reaction and the Wittig reaction above (Scheme 4.14) that the DOX ring is not stable under alkaline conditions. For this reason, we turned towards preparing vinyl-DOX from racemic vinyl glycolic acid (**4.59**). Vinyl glycolic acid is commercially available, but it is relatively expensive. However, it can be prepared by acidic hydrolysis of 2-acetoxy-3-butenenitrile (**4.77**) which can be synthesised from cheap starting materials; acetic anhydride (**4.75**) and acrolein (**4.76**) (Scheme 4.17)[65]. A nucleophilic reaction between sodium cyanide and acrolein will produce in-situ 2-hydroxypropenenitrile which in turn attacks acetic anhydride to produce 80 % yield of **4.77**. The acidic hydrolysis of the nitrile and the ester of **4.77** led to 95% yield of **4.59**.[65,66] Vinyl-DOX (**4.70**) ring was then formed by reacting **4.59** with paraformaldehyde under acidic conditions.



Scheme 4.17 A three-step reaction of vinyl-DOX from acetic anhydride and acrolein.

It was noticed that vinyl glycolic acid is not soluble in the common DOX synthesis solvents; cyclohexane, benzene or toluene.[36,37] For this reason, the reaction was carried out in 1,2 dichloroethane (DCE) to afford 70% of racemic vinyl-DOX (**4.70**). The largest reaction scale was made collected ~18 g of crude vinyl-DOX, which was dried over calcium hydride (CaH_2) and purified by distillation at 50 °C under vacuum (2 mbar) to afford ~16 g of pure vinyl-DOX as a colourless liquid. The structure has been confirmed by the proton and carbon NMR spectroscopy (Figures 4.7 and 4.8).

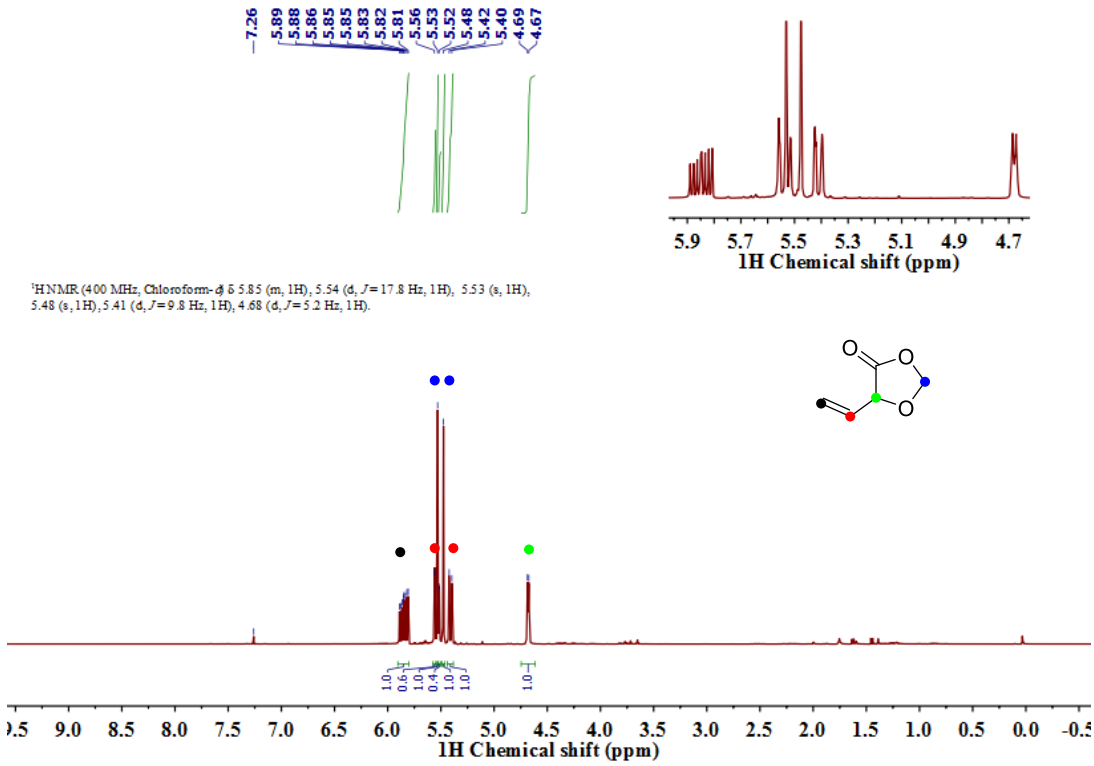


Figure 4.7 ^{1}H-NMR spectrum (*CDCl*$_3$, 400 MHz) of racemic vinyl-DOX (**4.70**).

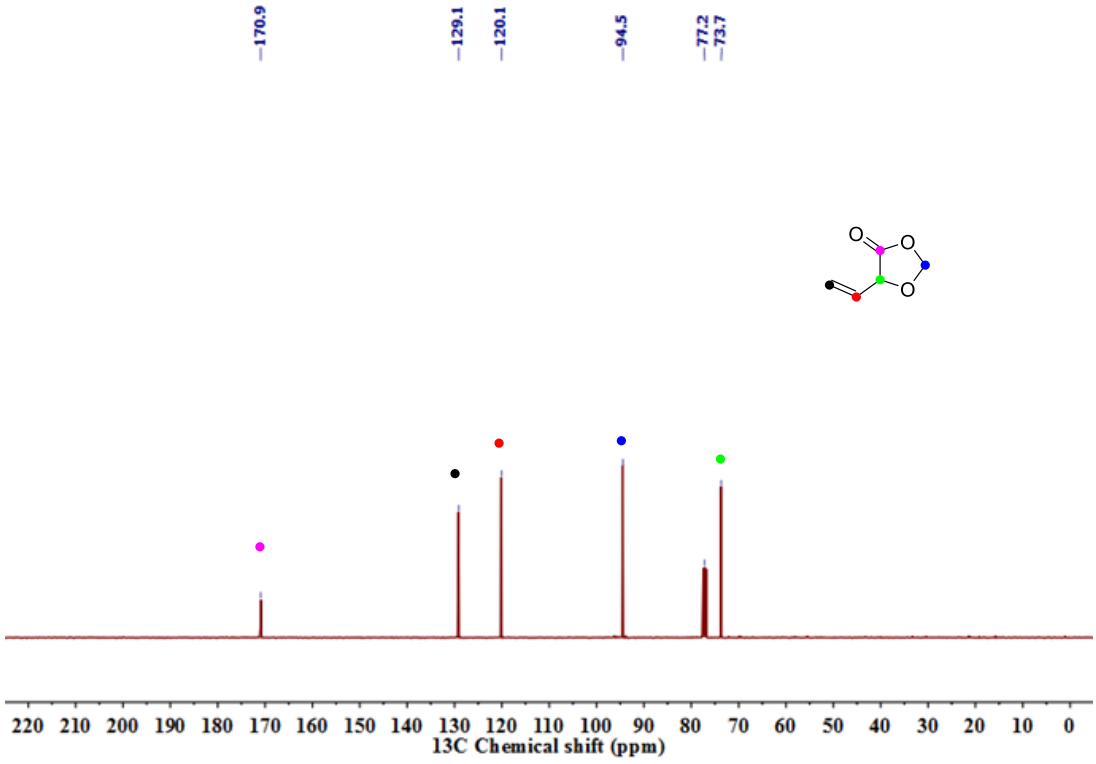


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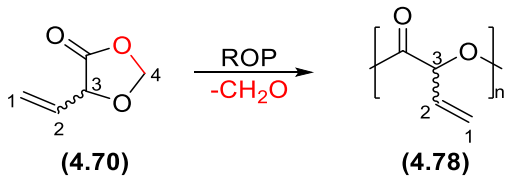
Figure 4.8 ^{13}C-NMR spectrum (*CDCl*$_3$, 100.2 MHz) of racemic vinyl-DOX (**4.70**).

This novel monomer can be used for a wide range of pre- and/or post- polymerisation functionalisation to afford new functionalised monomers and functionalised PAHAs. However, this monomer is racemic, so ring-opening polymerisation of **4.70** with release of formaldehyde will lead to an atactic PVGA as a precursor of atactic cyclopolyesters.

4.8 ROP of vinyl-DOX towards PVGA

Ring-opening polymerisation of DOX monomers was developed by the Shaver group using aluminium-salen catalysts.[36] The best results in terms of monomer conversion, polymer dispersity were by using **4.30, 4.31** and **4.32** catalysts. Based on this, these three catalysts were explored for the ROP of vinyl-DOX (**4.70**) with a variety of polymerisation conditions. Polymerisations were halted by cooling and adding several drops of methanol to quench the reaction. A crude sample was removed and dissolved in $CDCl_3$. The monomer conversion was calculated *via* ^{1}H-NMR spectroscopy. In the crude ^{1}H-NMR spectra, the CH peaks (peak 2 - Scheme 4.18**)** attributed to the monomer and to the polymer were overlapped at 5.80-6.20 ppm. Thus, this area was normalised to 100 and the integration of the the CH peak attributed to the monomer (peak 3 - Scheme 4.18) at 4.68 ppm was measured. For instance, in 50% conversion the ratio was 100 at 5.80-6.20 ppm to 50 at 4.68 ppm.



Scheme 4.18 Ring-opening polymerisation of vinyl-DOX monomer and releasing formaldehyde.

In general, the polymerisation rate of vinyl-DOX by **4.31** catalyst was slower in benzene than in bulk (Table 4.1 - entries 1-4). After around 3 days, only 27% conversion was obtained when the polymerisation was conducted in benzene. On the other hand, 47% conversion was achieved within two days when the reaction was performed in bulk (entry 7). Increasing the temperature to 130 °C increased the polymerisation rate as 50% of the monomers were polymerised within 24 hours. The polymerisation was also performed by using less sterically hindered ligands (**4.30** and

4.32 catalysts) (Table 4,2). Here, high conversions (>90%) were obtained with these two catalysts within 24 hours. The chloro-substitued catalyst (**4.30**) enhanced the rate probably due to the inductive electron-withdrawing group compared to the *tert*-butyl group of **4.31**.

Table 4.1: Polymerisation of vinyl-DOX (**4.70**) in Schlenk tubes under nitrogen using **4.31** catalyst.

Entry	Solvent	Temp. (°C)	Time (h)	Con. (%)[b]
1	Benzene[a]	60	48	19
2		90	5.5	14
3			27	11
4			70	27
5	Bulk	rt	48	12
6		60		18
7		90		47
8		130	7	44
9			24	50

Monomer: catalyst: BnOH = 50:1:1. [a] Monomer concentration in benzene = 2 M. [b] Monomer conversion determined as detailed above.

Also, the rate was faster even at 90 °C by using **4.32** catalyst. However, the molecular weights of the polymers produced were lower than the theoretical ones. This probably refers to the side reactions that will be discussed below. Expulsion of formaldehyde was observed directly by the formation of paraformaldehyde on the walls of the reaction vessel. However, the quantity of the condensed paraformaldehyde on the walls of the reaction vessel (Table 4.2 – entry 6) was significantly less than that in (Table 4.1 - entry 9 and Table 4.2 - entry 5) as you can see in Figure 4.9.

Table 4.2: Polymerisation of vinyl-DOX (**4.70**) in Schlenk tubes under nitrogen using **4.30** and **4.32** catalysts.

Entry	Catalyst	Temp. (°C)	Time (h)	Con. (%)[a]	$M_{n,th}$[b]	M_n[c]	$Đ$[c]
1	**4.30**	rt	48	12	-	-	-
2		60	48	18	-	-	-
3		90	48	47	-	-	-
4			72	66	2880	1520	1.42
5		130	24	91	3880	1650	1.51
6	**4.32**	90	24	93	4010	1710	1.66

Monomer: catalyst: BnOH = 50:1:1. [a] Monomer conversion determined from crude ^{1}H-NMR spectrua as detailed above. [b] $M_{n,th}$ (g/mol) = ([M]/[BnOH]) ×M_W(monomer) ×(% con.) + M_W(end group). [c] $Đ$ and M_n (g/mol) determined by gel permeation chromatography *vs.* polystyrene standard curve.

Figure 4.9 The Schlenk tubes of reactions (14-left and 15-right) at the end of the reaction to show the difference between the condensed paraformaldehyde on the walls of the reaction vessels.

The resulting polymer of entry 5 (Table 4.2) did not precipitate in a cold poor solvent (methanol or hexane), so the crude polymer was purified by Sephadex column to give yellowish oil. The ^{13}C-NMR spectrum of the purified product confirmed the formation of the desired polymer by disappearance of the CH_2O monomer peak that was at 94.5 ppm (Figure 4.10). However, the ^{1}H-NMR spectrum of entry 5 (Table 4.2) showed several unexpected peaks (Figure 4.11). We found that these polymerisation conditions induced competing side reactions. First, some of the vinyl group was isomerised to show peaks at 6.83 and 1.76 ppm.

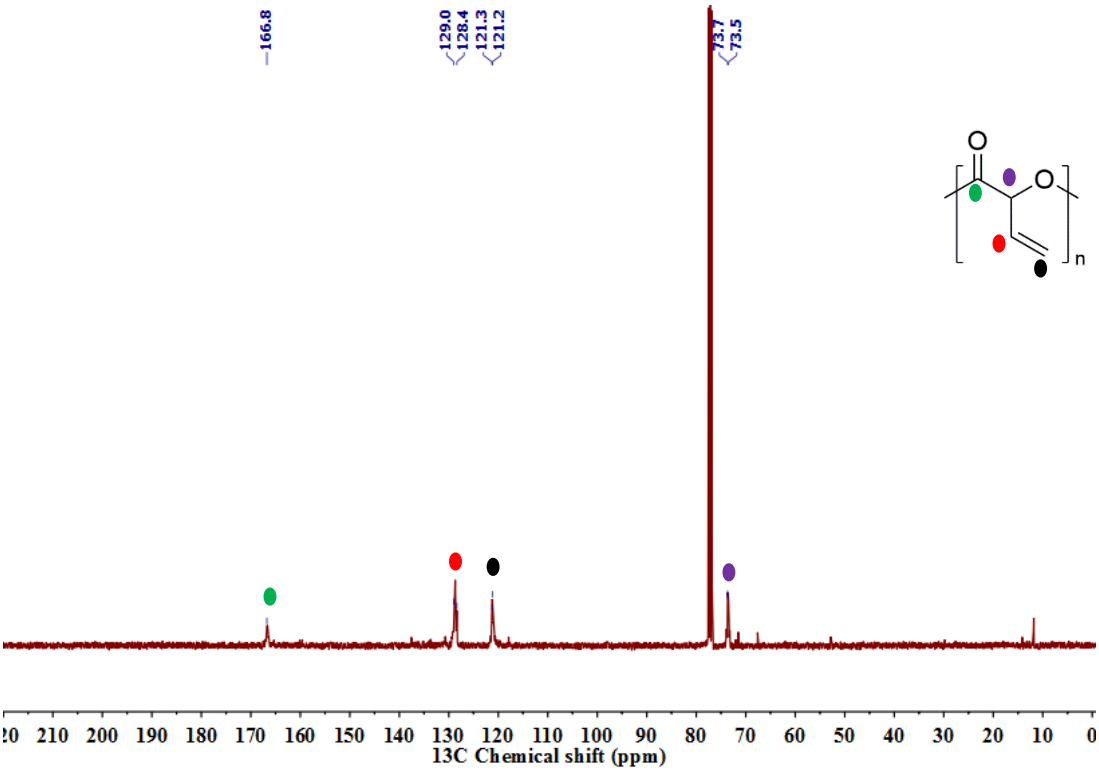
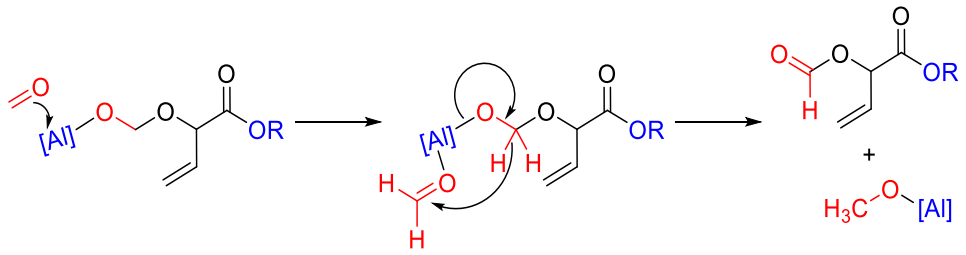


Figure 4.10 ^{13}C-NMR spectrum (*$CDCl_3$*, 100.2 MHz) of the produced polymer (entry 5 - Table 4.2).

Also, the peak at 4.81 ppm probably corresponds to an acetal group (-OCH_2O-) that could be formed if the formaldehyde did not leave the cyclic monomer during the polymerisation. The olefin isomerisation was minimised (reduced from 16% to 2%) by conducting the reaction at a lower temperature, 90 °C in entry 4 (see top spectrum in Figure 4.13). However, reducing the percentage of the formed polyester acetal was not successful even when the polymerisation was performed under static vacuum to force the release of formaldehyde from the reaction mixture. When the formaldehyde remains present in solution, the acyl ester chain end can also act as a trigger for a competing Tishchenko reaction acting as a chain transfer process and reducing molecular weights (Scheme 4.19). This also explains the reason for forming unexpected end groups such as formate or methyl in the catalytic polymerisation cycle.[37]



Scheme 4.19 The competing side reactions of ROP of DOX monomers.[37]

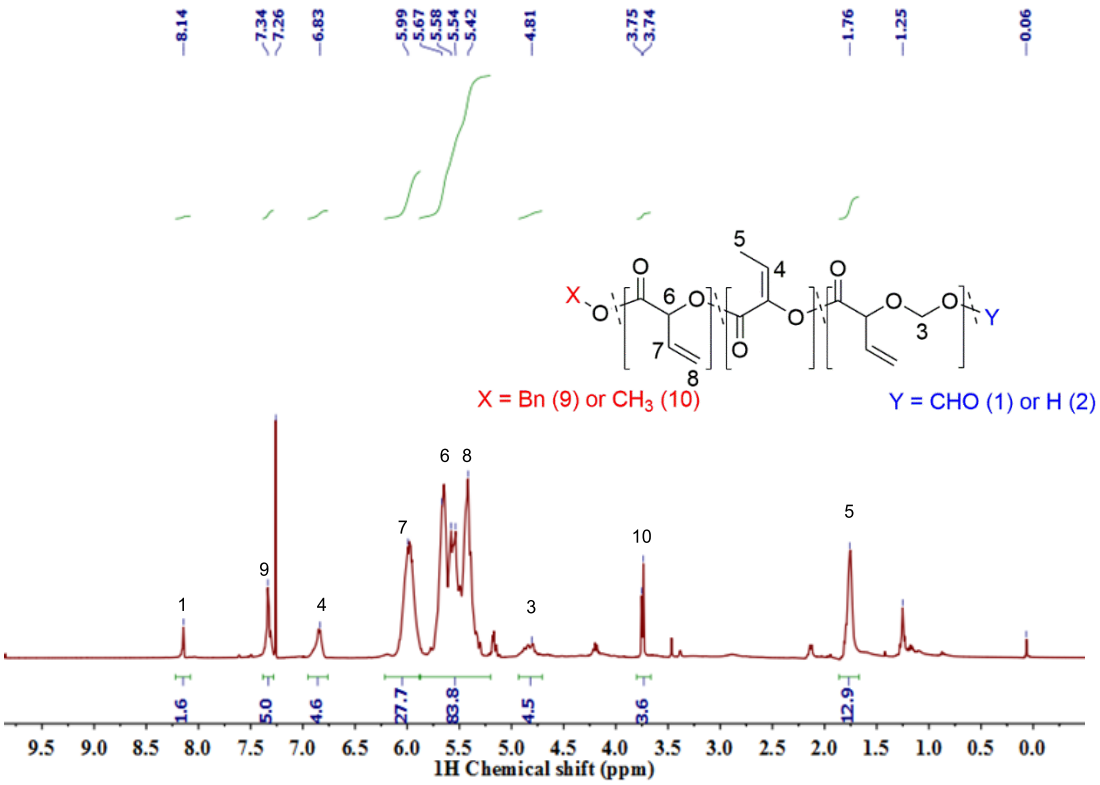


Figure 4.11 ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the produced polymer (entry 5 - Table 4.2).

However, the product of entry 6 (Table 4.2) was a white solid and the ^{1}H-NMR spectrum showed that it is probably a polyesteracetal (Figure 4.12).

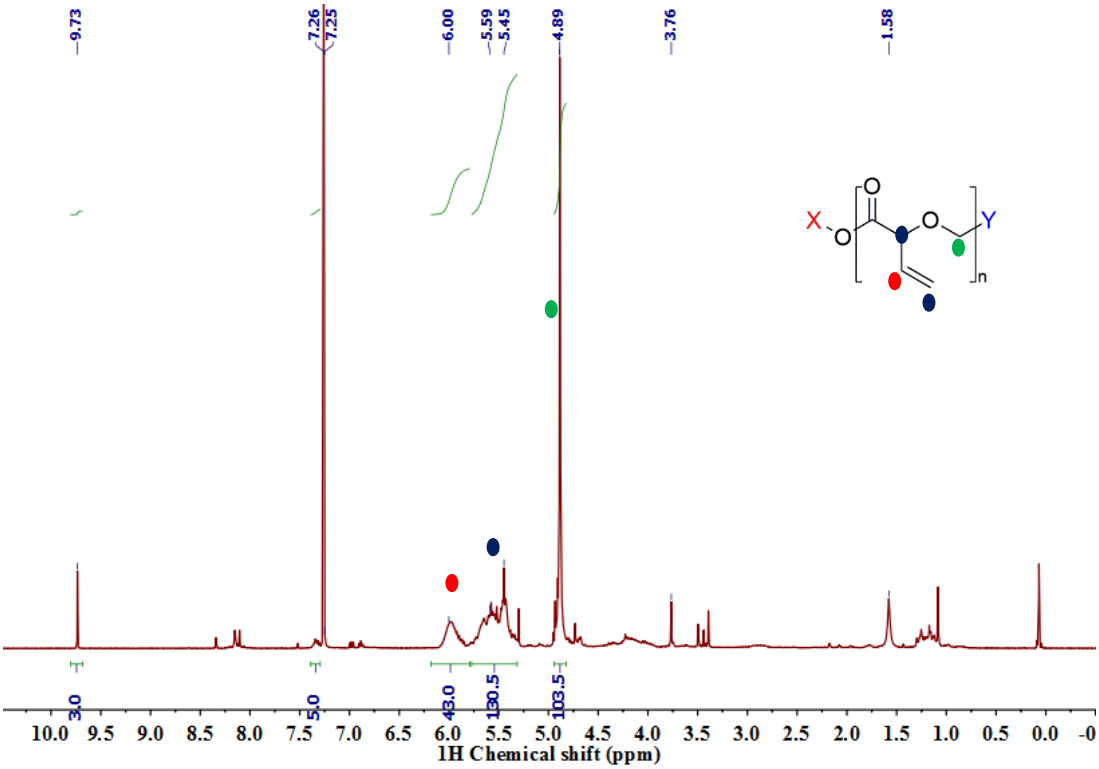


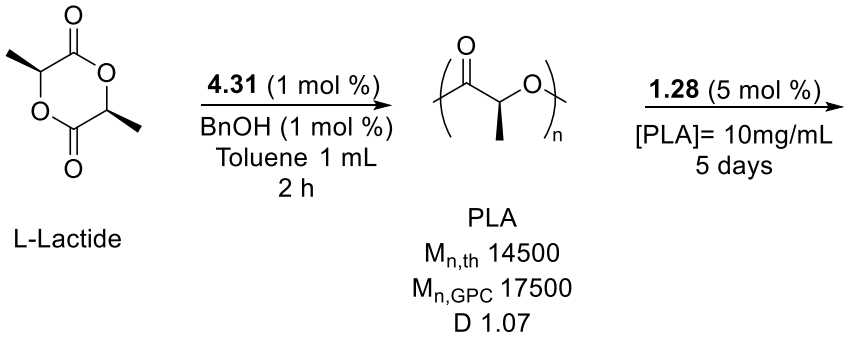
Figure 4.12 ^{1}H-NMR spectrum (*CDCl*$_3$, 400 MHz) of the produced polymer (entry 6 - Table 4.2).

This explains why this reaction did not yield the expected amount of the condensed paraformaldehyde on the walls of the reaction vessel (Figure 4.9). This product was poorly soluble in several solvents but its solubility in $CDCl_3$ was improved by sonication, but not enough to record a ^{13}C-NMR spectrum. For this reason, the optimum polymerisation condition was using **4.30** catalyst at 90 °C for three days (entry 4 -Table 4.2) and this was chosen to prepare samples of PVGA for the next reaction step. Even though a homo PVGA (**4.78**) was not obtained due to the presence of traces of acetal linkages (5%), the resulting polymer was treated by the 2nd generation Hoveyda-Grubbs catalyst **(1.30)** to investigate the possibility of forming the cyclo-polyester.

4.9 Ring-Closing Metathesis of PVGA

Ring-closing metathesis of simple diene-esters to generate unsaturated lactones has been extensively explored.[67,68] Also, cross-metathesis reactions of polyesters has been

investigated by the Shaver and Prunet groups. However, the cross-metathesis reactions of polyesters were conducted at relatively low temperatures (40 °C) for 70 hours.[79,70] We noticed in chapter two that RCM of PEB (**2.16**) takes several days for completion due to the slow re-metathesis stage. For this reason, PLA was used to test the PAHAs stability under the metathesis reaction conditions for 5 days at 40 and 84 °C using dichloromethane and 1,2-dichloroethane (DCE) as solvents, respectively.



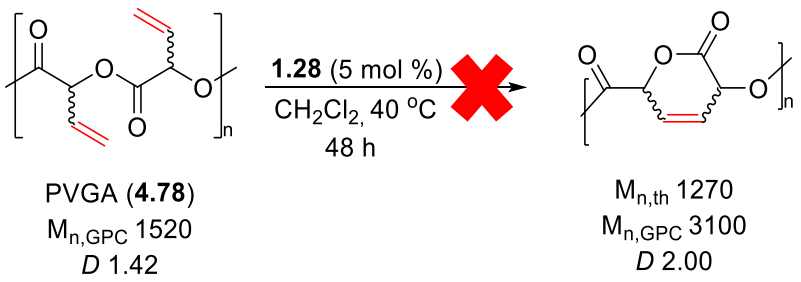
Scheme 4.20 PLA preparation by L-Lactide to test PLA stability in metathesis conditions for 5-days reaction.

Table 4.3: The molecular weight of PLA ($M_{n,GPC}$ 17500, *Đ* 1.07) after treating with metathesis catalyst **1.30** for 5 days at 40 °C in DCM.

Entry	Temp. (°C)	Solvent	M_n [a]	M_w [a]	*Đ* [a]
1	40	DCM	14400	18700	1.3
2	84	DCE	10600	19800	1.86

[a] *Đ*, M_w and M_n (g/mol) of the resulting polymer after the metathesis reaction determined by gel permeation chromatography *vs.* polystyrene standard curve.

While PEB was stable under the relatively harsh conditions of the metathesis reaction (up to eight days at 84 °C), the results of table 4.3 showed that PLA is degradable under these conditions, proved by a broaden dispersity of the resulting polymer with a lower molecular weight M_n. Obviously, the degradation rate was slower at the lower temperature. For this reason, the previously obtained PVGA was treated at 10 mg/mL in DCM with 5 mol % of **1.30** at 40 °C under static vacuum for two days only (Scheme 4.21). The reaction was terminated by a few drops of ethyl vinyl ether and the mixture was stirred for an extra hour. The crude mixture was concentrated under vacuum and purified by Sephadex column. The volatiles were evaporated to yield a brown solid. It was thought that two days are enough to complete the reaction as the molecular weight of the staring PVGA was relatively low (1520 Da).



Scheme 4.21 Metathesis reaction of PVGA.

However, the reaction was not completed as the CH_2 of the olefin group was noticed in the ^{13}C-NMR spectrum. Also, it was hard to calculate the conversion rate due to the overlapping between the peaks in the ^{1}H-NMR spectrum (Figure 4.13). Moreover, the molecular weight and the dispersity of the resulting polymer increased significantly from 1.42 to 2.00. This probably corresponds to cross-metathesis between the starting PVGA chains (intramolecular).

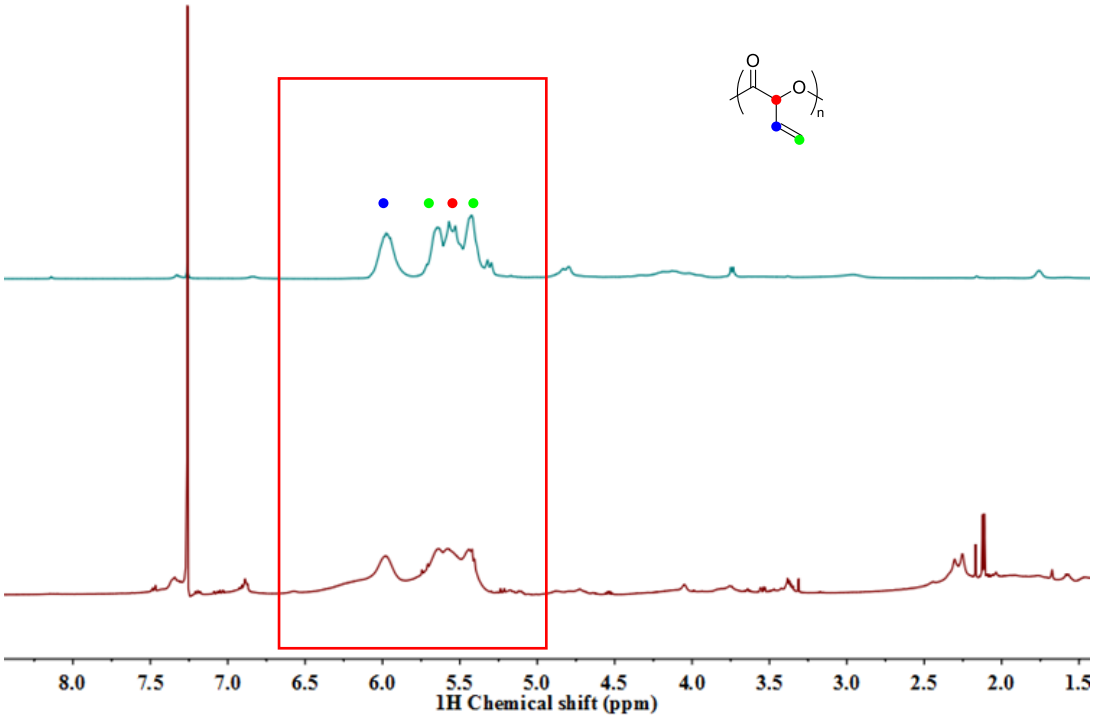


Figure 4.13 ^{1}H-NMR spectra (*CDCl*$_3$, 400 MHz) of the PVGA (Table 4.2 - entry 4) in the top, and the metathesis product of the reaction in scheme 4.21.

For this reason and due to the limitation of the work time, the development of this work was stopped at this stage.

4.10 Conclusion

Several attempts were tried to afford a precursor monomer of poly(vinyl glycolic acid) (PVGA) and the highest yield was obtained by preparing vinyl-DOX monomer (**4.70**). This novel functionalsable monomer can be used for a wide range of pre- and/or post-polymerisation modification to afford new functionalised monomers and functionalised PAHAs. However, an enantiopure version of **4.70** was not obtained at this stage.

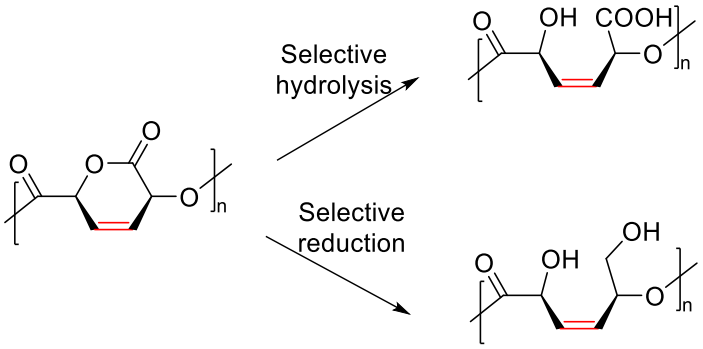
Vinyl-DOX monomer was polymerised by Al-Salen catalysts system to afford either PVGA or the polyesteracetal derivative. However, only low molecular weights of polymers with relatively high dispersities were afforded.

The obtained PVGA was treated with the 2nd generation Hoveyda-Grubbs catalyst for 2 days only and at relatively low temperature due to the degradability of the ester group at harsher conditions. The reactions showed that some of the olefin groups were metathesised but unfortunately the reaction was not complete. Under the used metathesis conditions, the olefin of atactic PVGA presumably behaved as a Type II olefin. However, changing the reaction conditions or the configurations of the olefins would make it as a Type I.

4.11 Future work

Since vinyl-DOX can be easily made from vinyl glycolic acid, enantiopure vinyl-DOX can also be made from enantiopure precursors. Thereby, starting the synthesis from enantiopure 2-hydroxypropenenitrile, a precursor of 2-acetoxy-3-butenenitrile, will afford enantiopure products. Enantioselective cyanosilylation of aldehydes has been reported in several works.[71-72] In particular, enantioselective cyanosilylation of acrolein catalysed by titanium tetra-*iso*-propoxide [Ti(O-*i*-Pr)$_4$] and chiral Schiff bases afforded an enantioenriched 2-hydroxypropenenitrile.[71]

In addition, once the RCM reaction conditions are optimised to have the desired cyclopolyester, the resulting lactone units can be either hydrolysed[73] or reduced[74] selectively. These reactions would produce unsaturated polyesters with alternating sequences of either -COOH and -OH, or diols pendents which cannot be obtained by conventional polymerisation methods.



Scheme 4.22 Possible selective lactone ring opening reactions.

4.12 References

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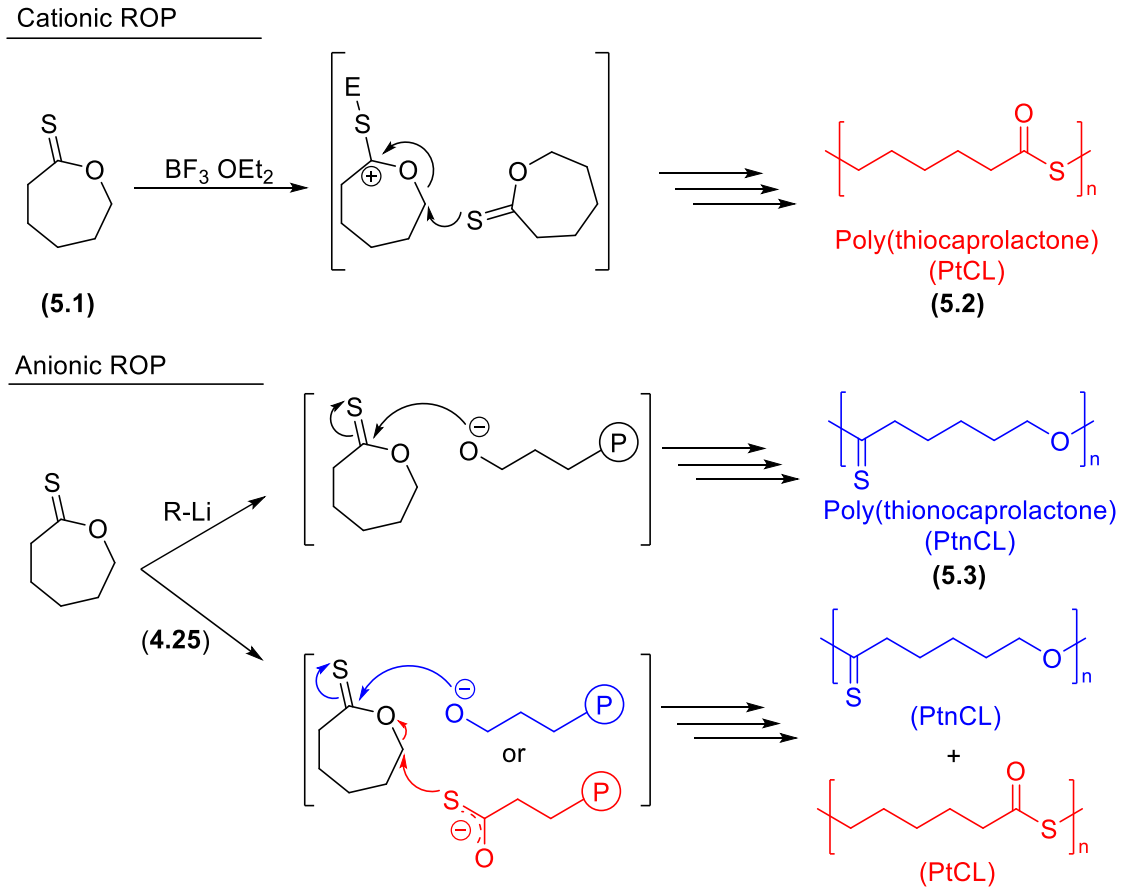
Chapter 5. Regioselective ROP of thionolactones

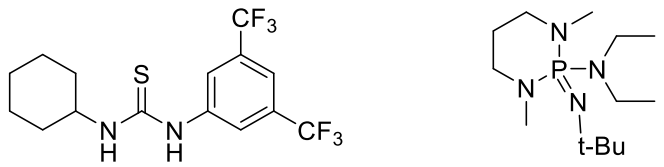
5.1 Introduction

While five-, six-, and seven-membered thionolactones have been synthesised by several methods,[1,2] only a few papers detailing the polymerisation of ε-thionocaprolactone have been reported so far. Cationic ring-opening polymerisation of ε-thionocaprolactone (ε-tnCL - **5.1**) proceeds with inversion of the thionoester to thioester and generates poly(thiocaprolactone) (PtCL – **5.2**) previously reported by the Endo group.[3] On the other hand, the anionic polymerisation with organolithium and Grignard reagent initiators selectively afforded the polymer consisting of thionoester unit, poly(thionocarpolactone) (PtnCL - **5.3**), with quantitative monomer conversion (Scheme 5.1).[3-8]



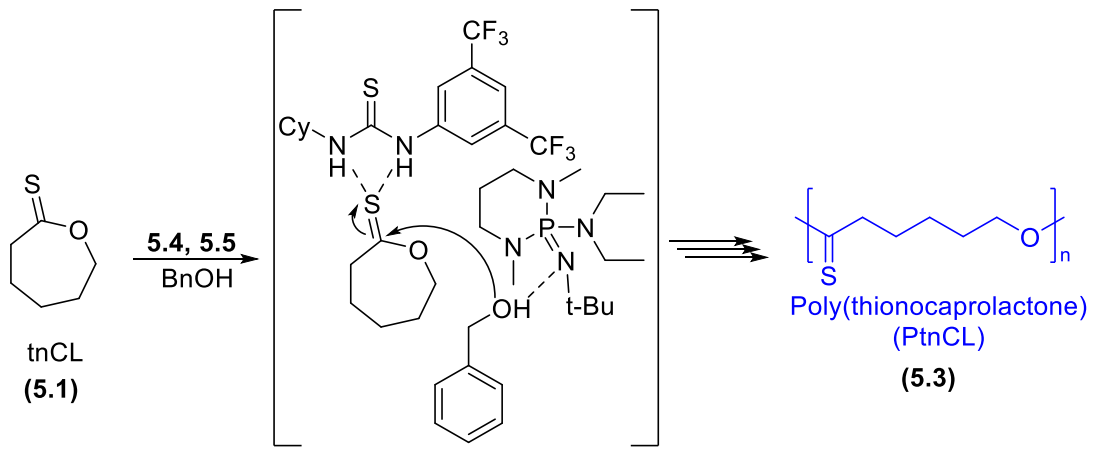
Scheme 5.1 Endo's cationic and anionic ROPs of ε-tnCL.[3-8]

However, partial inversion of the S/O substitution occurs with weak nucleophiles (DBU - **4.25**), resulting in a mixed polymer backbone.[4-7] Recently, use of basic organocatalysts by the Kiesewetter group allowed for the retention of the S/O substitution and controlled generation of homopoly(thionocaprolactone) (**5.3**).[8] The ROP by base catalysts alone is hypothesised to proceed *via* a nucleophilic mechanism, while the addition of an H-bond donating thiourea (TU, **5.4**) is shown to provide excellent reaction control. The presence of thiourea has a distinct impact upon the base cocatalysed ROP of tnCL. The TU/DBU (5 mol % each) cocatalysed ROP of tnCL from octadecylthiol in C_6D_6 lowered the reaction time and dispersity versus the ROP with DBU alone. The increased reaction control provided by **5.4** could arise from the suppression of transesterification events due to prominent secondary interactions. The most striking results are observed with 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP – **5.5**), which exhibits no activity in the absence of TU, but the TU:BEMP (5 mol % each) catalysed ROP of tnCL (2 M, 1 equiv) from benzyl alcohol (1 mol %) achieves full conversion in 5 h (Scheme 5.2).[8]



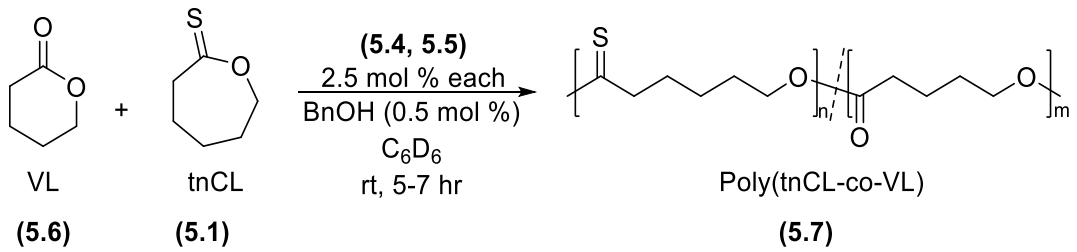
Thiourea (TU) **(5.4)** BEMP **(5.5)**

Figure 5.1 The chemical structures of thiourea and BEMP used in ROP of tnCL.



Scheme 5.2 Proposed mechanism for the H-bond-mediated ROP of tnCL [82]

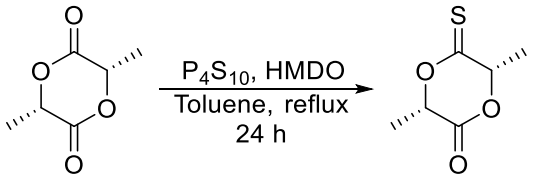
This activation of **5.4** to tnCL could be due to increased electrophilicity of the carbon of the C=S bond as the electrostatic charges at the carbon and polarity of the C=S bond increase by ~5−10% upon the binding of **5.4**. These results suggest that ROP of tnCL is operative by dual activation of monomer by **5.4** and of chain-end base. The first copolymer of thionoester and ester units was prepared by a copolymerisation of tnCL and δ-valerolactone (VL – **5.6**) (Scheme 5.3). Kinetically, tnCL is more reactive than VL. VL will not undergo ROP in the presence of DBU alone, and the increased reactivity of tnCL *vs* VL is attributed to the difference in the electron delocalisation between the lactone and the thionolactone groups. This difference comes from the difference between the oxygen and sulfur electronegativity as sulfur is much less electronegative than oxygen. However, when **5.4** and **5.5** (2.5 mol % each) is added to a mixture of VL (1 M, 0.5 equiv), tnCL (1 M, 0.5 equiv) and benzyl alcohol (0.5 mol %) in C_6D_6, both monomers are observed to undergo ROP at approximately equal rates in a first-order evolution of [monomer]s *vs* time plot (ktnCL/kVL = 1.07), suggesting random copolymer formation.[8]



Scheme 5.3 Ring-opening copolymerisation of tnCL and VL.[82]

Incorporating tnCL with VL is associated with reduced hydrolytic stability under basic conditions, increased stability toward hydrolysis under acidic conditions, and minimally altered stability in neutral water. These observations are consistent with general trends of thionoester stability.[8]

While the ring-opening polymerisation of lactide (LA) to poly(lactide) (PLA) is well documented, the derivatisation of lactide as a platform to other polymers is extremely rare. The Pietrangelo group synthesised 1,4-dioxan-2-one, *S,S*-3,6-dimethyl-5-thioxo monomer (L-thionolactide **- 5.8**) according to Scheme 5.4 by reacting L-LA with a reagent combination of phosphorous pentasulfide (P_4S_{10}) and hexamethyldisiloxane (HMDO).[9-11]



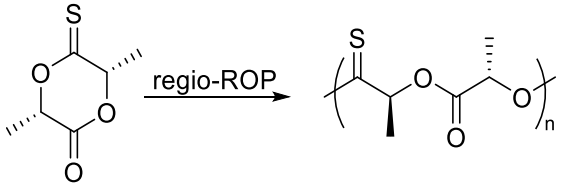
L-lactide L-thionolactide
(5.8)

Scheme 5.4 L-thionolactide preparation from L-lactide.[9]

However, homopolymerisation of L-thionolactide by the Pietrangelo group was not successful. The monomer has two active sites that the initiator or the propagating chain end can attack (thionolactone and lactone), and this led to a non-controlled structure. They used several catalytic systems such as 4-dimethylaminopyridine (DMAP), tin (II) 2-ethylhexanoate (**4.23**), diphenylphosphate (DPP), TBD (**4.24**), and DBU (**4.25**) in the presence and absence of thiourea (**5.4**) with different reaction conditions to achieve ROP of (**5.8**). All these attempts led to either no reaction or low monomer conversion with a non-controlled structure confirmed by broad peaks observed in ^{1}H-NMR spectra of the resulting products.

5.2 Aims and objectives

To the best of our knowledge poly(tnCL-co-VL), the random copolymer prepared by the Kiesewetter group, is the only reported polymer made of thionoester and ester linkage units. Thus, a regioselective ring-opening polymerisation (regio-ROP) of L-thionolactide (**5.8**) to poly(L-thionolactide) (**5.9**) will give the first controlled structure polymer made of alternate thionoester and ester monomer units (Scheme 5.5).



(5.8) **(5.9)**

Scheme 5.5 Regioselective ROP of L-thionolactide to afford poly(L-thionolactide).

We were asked by the Pietrangelo group to explore this polymerisation with our family of Al-salen catalysts.

5.3 Regioselective ROP of thionolactide

The L-thionolactide monomer (**5.8**) was provided by the Pietrangelo group and purified by crystallisation from hexane to afford yellowish crystals. The polymerisation conditions were varied using BnOH as an initiator and **4.30** and **4.31** as catalysts. While L-lactide is fully polymerised with **4.31** at 120 °C for 17 h, L-thionolactide conversion was 27% only after 72 h. The new peaks that appeared in the ^{1}H-NMR spectrum confirmed that the reaction conditions yielded a non-controlled structure. Furthermore, conducting the polymerisation for 17 h at a lower temperature (55 °C) using **4.30** and **4.31** catalysts yielded 4 and 1% conversion, respectively (Table 4.5). Monomer conversion was determined from the crude ^{1}H-NMR spectra using the relative integrations of -CH(O-ester) peak attributed to the polymer (**5.9)** at 5.68 ppm and the -CH(O-ester) peak attributed to the monomer (**5.8**) at 3.83 ppm (Figure 5.2).

Table 5.1: Polymerisation of L-thionolactide (**5.8**) in Schlenk tubes under nitrogen using **4.30** and **4.31** catalysts.

Entry	Catalyst	Tem.(°C)	Time (h)	Con.(%)[a]
1	**4.31**	120	72	27
2		55	17	1
3	**4.30**	55	17	4

[Monomer]:[Catalyst]:[Initiator] ratio 100:1:1, $[Monomer]_0$ = 1 M in toluene, [a] Monomer conversion determined from crude ^{1}H-NMR spectra as detailed above.

In the second set of attempts, an excess of catalyst, *vs* monomer and initiator, was used (Table 5.2). Here, the [monomer]:[catalyst]:[initiator] ratio was 100:4:1. Conducting the polymerisation at 85 °C and 33 °C showed poor conversions (Table 5.2 – entries 2, 3 and 5). However, the polymerisation by the two used catalysts (**4.30** and **4.31**) surprisingly proceeded much faster at 55 °C to yield 89% conversion with **4.30** within 3 h and 40% with **4.31** within 17 h (Table 5.2 - entries 1 and 4). The produced polymers were purified by precipitation in cold methanol to yield a white solid of the desired poly(thionolactide) (**5.9**). This was confirmed by the NMR spectroscopy (Figures 5.2 and 5.3) by showing sharp corresponding peaks. The ^{1}H-NMR spectra of the products showed only two new deshielded sharp quartet proton peaks corresponding to the two methine protons of the polymer (thionoester and ester).

Table 5.2: Polymerisation of L-thionolactide (**5.8**) in Schlenk tubes under nitrogen using an excess of catalysts **4.30** and **4.31**.

Entry	Catalyst	Tem.(°C)	Time (h)	Con.(%)[a]
1	**4.31**	55	17	40
2		85		8
3	**4.30**	33	3	4
4		55		89
5		85		6

[Monomer]:[Catalyst]:[Initiator] ratio 100:4:1, $[Monomer]_0$ = 1 M in toluene, [a] Monomer conversion determined from crude ^{1}H-NMR spectra as detailed above.

This confirmed that an excess of catalyst is playing a mechanistic role by activating the thionolactone site and making it more electrophilic towards the nucleophilic attack as thiourea (**5.4**) did with ε-thionocaprolactone (**5.1**) above. The polymerisation convertion did not exceed more than 51% after 168 h when **4.31** catalyst was used affording a narrow disperse polymer (Table 5.3 – entry 4). On the other hand, extending the polymerisation time from 4 h to 7 h completed the polymerisation when **4.30** catalyst was used (Table 5.3 – entry 6). However, this resulted in a lower molecular weight polymer and a higher dispersity. This probably due to increasing the transesterification rate when most of the monomers are consumed in the reaction.

Table 5.3: Polymerisation of L-thionolactide (**5.8**) in Schlenk tubes under nitrogen using extra catalysts **4.31** and **4.30** at 55 °C.

Entry	Catalyst	Time (h)	Con.(%)[a]	$M_{n,th}$ [b]	M_n [c]	$Đ$[c]
1	**4.31**	13	32	-	-	-
2		17	40	-	-	-
3		45	46	-	-	-
4		168	51	8260	5300	1.15
5	**4.30**	4	89	14350	21280	1.32
6		7	>99	16100	11480	1.47

[Monomer]:[Catalyst]:[Initiator] ratio 100:4:1, $[Monomer]_0$ = 1 M in toluene, [a] determined by ^{1}H-NMR spectroscopy as detailed above. [b] $Mn = M_w[monomer] \times con.(\%) + M_w(BnOH)$; [c] M_n and $Đ$ determined by GPC vs uncorrected PS standard.

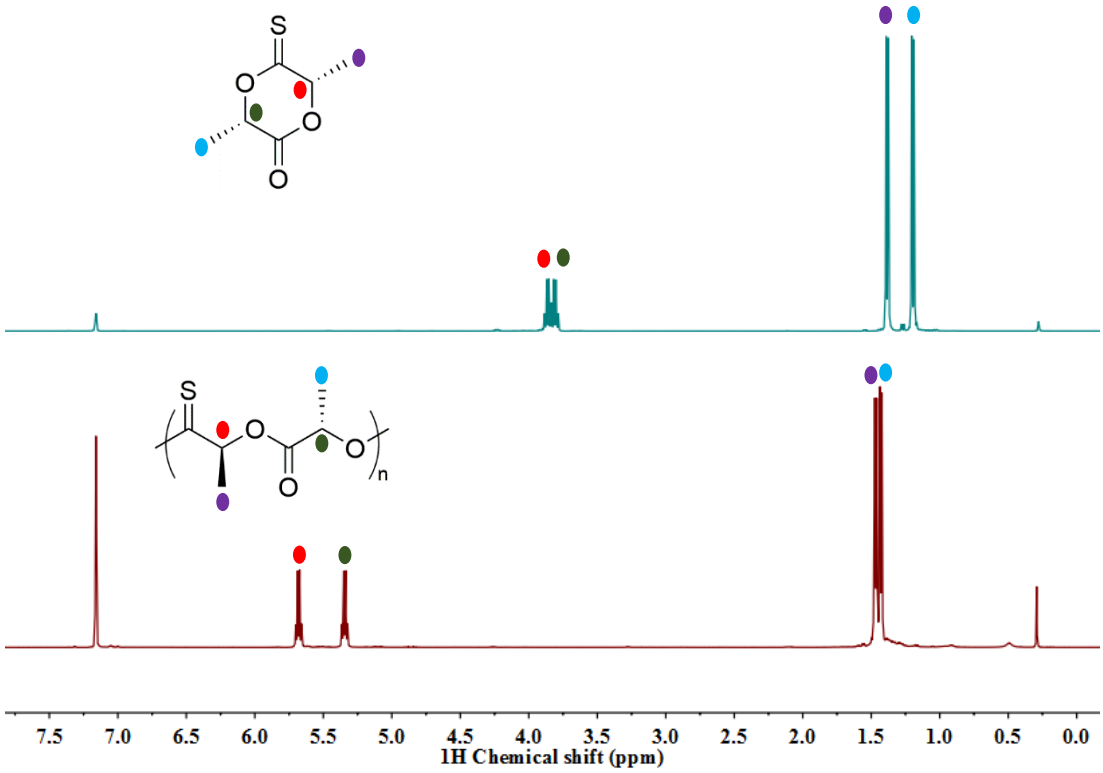


Figure 5.2 ^{1}H-NMR spectra (C_6D_6, 500.2 MHz) of L-thionolactide (top) and poly(L-thionolactide). (bottom)

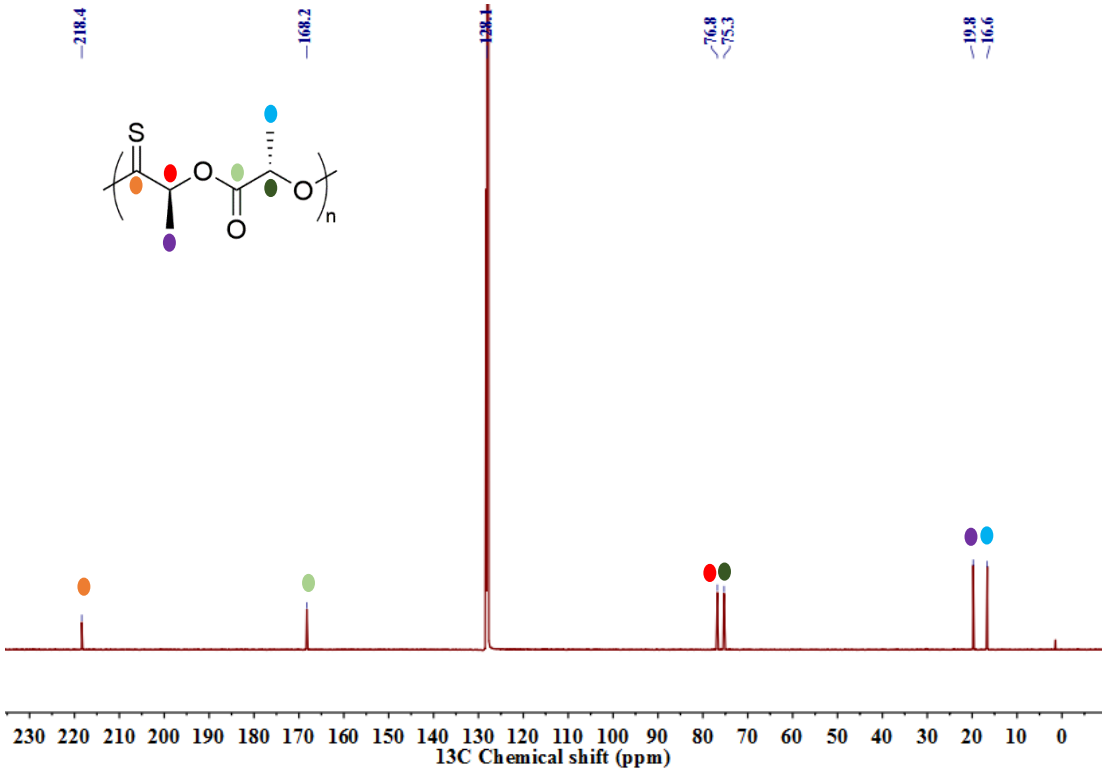


Figure 5.3 ^{13}C-NMR spectrum (C_6D_6, 125 MHz) of poly(L-thionolactide) (**5.9**).

This regioselective ring-opening polymerisation of L-thionolactide proceeded without inversion of the thionoester to thioester and generated only a thionoester group in the polymeric structure. This is confirmed by the ^{13}C-NMR spectrum (Figure 5.3). The researchers, who reported poly(thiocaprolactone) (PtCL – **5.2**) and poly(thionocaprolactone) (PtnCL – **5.3**), distinguished between the thionoester and thioester by two main characterisation techniques; ^{13}C-NMR spectroscopy and Fourier-transform infrared spectroscopy (FTIR). All the reported data showed that the chemical shift in ^{13}C-NMR spectra of the thionoester was higher than the chemical shift of thioester, ~ 220 *vs* 200 ppm, respectively.[3-8] Since our poly(L-thionolactide) showed a single carbon peak close to 220 ppm (218.4 ppm), this means that this peak probably refers to the thionoester group. The functional group can also be confirmed by FTIR since the thioester has a strong IR carbonyl absorption at 1680 cm-^{1} while the thioester does not have this peak.

To understand the behaviour of these two catalysts, we conducted the following experiments. Two reactions were initiated by BnOH:**4.30** and one reaction was initiated by BnOH:**4.31** at the desired temperature 55 °C with a ratio of 100:1:1, monomer:catalyst:initiator (Table 5.4). After 17 h, a sample was taken from the three reactions' vessels and ^{1}H-NMR analysis of the crude showed only 4% and 1% conversions, respectively. Then, an extra 3 mol % of the catalyst **4.30** was added to reactions 1 and 3 (Table 5.4 - entries 1 and 3) and an additional 3 mol % of the catalyst **4.31** was added to the reaction 2 (Table 5.4 - entry 2).

Table 5.4: Polymerisation of L-thionolactide using extra catalysts **4.30** and **4.31**.

Entry	Catalyst	[M]:[C]:[I] mol %	Time (h)	Con.(%)[a]	Additional catalyst added mol %	Time (h)	Con.(%)[a]
1	**4.30**	100:1:1	17	4	3 of **4.30**	3	90
2				4	3 of **4.31**		19
3	**4.31**			1	3 of **4.30**		22

$[Monomer]_0$ = 1 M in toluene, [a] determined by ^{1}H-NMR spectroscopy by methine protons peak integration of the product. Temperature at 55 °C.

Surprisingly, the polymerisation rate increased significantly to afford 90% conversion in the reaction that contained an extra 3 mol % of the catalyst **4.30** that was initiated by BnOH:**4.30** system. However, the conversion after adding the same

type and amount the catalyst to the reaction that was initiated by BnOH:**4.31** (Table 5.4 - entry 3) was only 22% in the same period. Also, the conversion after adding an extra 3 mol. % of the catalyst **4.31** to the reaction that was initiated by BnOH:**4.30** was only 19%. The results of the three reactions confirm that excess of catalysts is playing as co-catalysts to activate the monomer and consequently speed up the polymerisation. However, the size of the steric ligand of the catalysts is important to enable both the initiator catalyst and the cocatalyst to come close together to activate the monomer and proceed the polymerisation. When the reaction was initiated by a small steric ligand of catalyst **4.30** (chloro-substituent) and then a small steric ligand of that catalyst was added, the polymerisation proceeded fast to around 90% within 3 h. However, when a bulky ligand catalyst **4.31** (*tert*-butyl substituent) was added to that system, the yield was around only 20%. Similarly, when the reaction was initiated by a bulky ligand catalyst **4.31** (*tert*-butyl-substituent) and then a small steric ligand of catalyst **4.30** was added, the polymerisation yield was also was around 20%.

5.4 Conclusions and Future work

L-thionolactide was successfully polymerised for the first-time using Al-Salen catalysts. The polymerisation was regioselective at the thionoester site of the monomer to afford a well-controlled structure polymer of poly(L-thionolactide). The polymerisation rate increased by adding an excess of catalysts (3 mol %), which probably played the role of "monomer activator". Relatively high molecular weights of the polymer with a full monomer conversion was observed within a few hours. The development of this work was stopped at this stage in the Shaver group and forwarded to the Pietrangelo group to perform further characterisation (FTIR) to confirm the structure, run a kinetic reaction and investigate the degradability and the thermal properties of this novel polymer.

5.5 References

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Chapter 6. Conclusions

The aim of this research was to use ring-closing metathesis (RCM) reaction in polymers with pendent olefin groups, to make unsaturated cyclopolymers. The efficiency of this reaction was dependent on:

1- the starting polymer; its stereoregularity, the type of olefin and its stability, and;
2- the reaction parameters; concentration, temperature, time, catalyst type and loading.

Starting polymers with pendent Type I olefin groups are favoured since this type of olefin can enter the RCM reaction reversibly, so the reaction continues until the most thermodynamically stable structure is reached.

In **Chapter two**, we have shown that RCM of linear, stereoregular polyethers with pendent olefins can be used to prepare cyclopolyethers with excellent control over the ring size. The reaction was divided into a fast metathesis and a slow rearrangement metathesis stage. This assumes that olefins in the starting polyether (poly-epoxybutene - PEB) behaved as Type I olefins. The isotactic PEB leads, after RCM, to a functionalisable cyclopolyether (FCPE) with well-defined *cis* substitution patterns. The glass transition temperature of the polymer increased significantly after RCM cyclisation, especially for the stereocontrolled structure. Both *S* and *R* configurations of FCPE were optically active, mirror images of each other and showed helical conformation structures in solution. FCPE was functionalized by dihydroxylation and this provided sugar-like structures with a poly(ethylene glycol) backbone that leads to a new PEGose architecture. By taking advantage of the diastereoselectivity of the subsequent dihydroxylation reaction, we were able to create a cyclopolymer where the configuration of all the stereogenic centres is controlled, and which mimics naturally occurring amylose. Also, the degree of the dihydroxylation was controlled to broaden the solubility of the resulting polymer and to leave olefin sites for further functionalisation.

In **Chapter three,** we proposed and synthesised a novel polymer with pendent olefins, poly(divinyl-oxirane) (PDVO), to be used as a precursor to make cyclopolymers by RCM. ROP of racemic divinyl oxirane by (TPP)AlCl as an initiator and MAlBP as a

monomer activator afforded a novel polymer. Also, a synthetic route to afford enantiopure divinyl oxirane was reported but the yield was relatively poor.

In **Chapter four**, a novel monomer of vinyl-DOX was synthesised and polymerised by Al-salen catalysts system to obtain poly(vinyl glycolic acid) (PVGA) as a platform for RCM reaction to afford biodegradable cyclopolyesters. However, only low molecular weights of PVGA with relatively high dispersities were afforded. Unfortunately, using the optimum conditions, that were used on PEB in Chapter 2, on PVGA did not yield the desired six-membered cyclostructure. This assumes that the olefin of atactic PVGA behaved as a Type II olefin under these conditions.

The work of this thesis has demonstrated that ring-closing metathesis can be used to make sterercontrolled cyclopolymers, which cannot be obtained easily by conventional polymerisation methods. This paves the way to afford cyclopolymers with a wide range of functional groups since these cyclopolymers are functionalisable through the resulting olefin. The continued research and development into cyclopolymers will play a big role in the drive towards polymers that mimic naturally occurring polymers. The pursuit of diversifying the functionalisable cyclostructures in order to provide a wide range of polymers having different properties is ongoing. Furthermore, this new unsaturated cyclopolymer platform offers significant potential for drug conjugation, and biomedical mimicry. The likelihood of using sterecontrolled cyclopolymers in drug delivery looks brighter with each academic publication in this field.

Chapter 7. Experimental

7.1 General methods and characterisation

All experiments involving air- and moisture-sensitive compounds were performed under a nitrogen or argon atmosphere using a Vigor glovebox system equipped with a -35 °C freezer and [H_2O] and [O_2] analysers or using standard Schlenk techniques. Dichloromethane (DCM), tetrahydrofuran (THF), hexane and diethyl ether, toluene were obtained from an Innovative Technologies solvent purification system incorporating columns of alumina or copper catalysts and were de-gassed by three freeze-pump-thaw cycles prior to use. Gel permeation chromatography (GPC) was performed using a Malvern Instruments Viscotek 270 GPC Max triple detection system with 2 × mixed bed styrene/DVB columns (300 × 7.5 mm) in THF at a flow rate of 1 mL min^{-1} and an injection volume of 100 μL or 200 μL. Samples for analysis were pre-dissolved in chloroform or THF at a concentration of 1-2 mg/L^{-1} for polyethers and ~8-12 $mg.mL^{-1}$ for polyesters. ^{1}H-NMR spectra were recorded at 298 K using BrukerAvance spectrometers (400, 500 or 600 MHz). ^{13}C-NMR spectra were recorded using BrukerAvance spectrometers (100-126 MHz). 2D NMR analyses (COSY and HSQC) were recorded using BrukerAvance spectrometers (500 or 600 MHz). Chloroform-d benzene-d_6, dichloromethane-d_2, D_2O or toluene-d_8 were used as solvents for all NMR analyses. The chemical shifts (δ) and coupling constants (J_{HH}) were recorded in parts per million (ppm) and Hertz (Hz) respectively. Differential scanning calorimetry (DSC) was carried out using TA Instruments DSC Q2500 through a heat/cool/heat cycle between -90 °C to 100 °C at a rate of 10 °C min^{-1}. Values of glass transition temperatures (T_g) were recorded from the second heating scan. The enantiomeric excess (ee) was determined by chiral HPLC using Agilent 1200 instrument and Chiralcel® OD-H column. The mobile-phase was hexanes:*i*-PrOH 95:5 at flow rate 1 mL min^{-1} at wavelength 230 nm. IR spectroscopy was performed using Shimadzu FTIR-8400S. The water-soluble polymers were dried using Alpha 1-4 LDplus Laboratory Freeze Dryer. The level of metals residues in the polymers was detected by inductively coupled plasma-optical emission spectrometry (ICP-OES) using an Agilent 7500ce (with Octopole reaction system), employing an

RF forward power of 1540 W and reflected power of 1 W, with argon gas flows of 0.81 $L.min^{-1}$ and 0.19 $L.min^{-1}$ for carrier and makeup flows, respectively. The masses analysed were 188Os and 189Os for Os and 98Ru for Ru. Each mass was analysed in fully quant mode (three points per unit mass). A series of standards were prepared using single element 1000 mg L^{-1} (Qmx) diluted with 2% /0.5 % v/v HNO_3/HCl to give a range of standards. The circular dichroism (CD) spectra were measured at room temperature using a Jasco J-810 spectropolarimeter and a 0.02 cm path length quartz cuvette with sample concentration 1 mg/mL in deionised water or methanol at measurement range 260-180 nm. The ultraviolet photomultiplier parameters were set as follows; data pitch 0.2 nm, slit width 1 nm, response scan rate 2 s. Two scans for each sample were collected at a rate of 10 nm/min.

7.2 Materials

Grubbs first-generation catalyst, Hoveyda-Grubbs second-generation catalyst, trimethylaluminium (2 M in toluene), diethylaluminium chloride (1 M in hexane), 1,2-dichloroethane (DCE), Pd (10 %)/C, osmium tetroxide, L-serine, benzyl bromide, para-toluene sulfuric acid monohydrate, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), *bis*(acetoxy)iodobenzene (BAIB), D-mannitol, triethylamine, tri-octylamine, Sephadex-LH 20, Sephadex G-25 and L-malic acid were purchased from Sigma-Aldrich and used as received. Di-*tert*-butyl dicarbonate, paraformaldehyde, methyltriphenylphosphonium bromide, borane tetrahydrofuran complex solution (1 M in THF), *o*-nitrophenyl selenocyanate, tri-*n*-butylphosphine, acetyl chloride and acetyl bromide were purchased from Acros Organics and used as received. Acrolein was obtained from Fluka. 1,3-diaminopropane, 3,5-di-*tert*-butylsalicylaldehyde, and 3,5-dichlorosalicylaldehyde were purchased from VWR International Ltd. and used as received. 3,4-Epoxy-1-butene, benzyl alcohol, chloroform-d_1 and 1,2-epoxy-5-hexene were purchased from Sigma Aldrich and dried over calcium hydride for 24 h under reflux and distilled under an atmosphere of nitrogen or vacuum prior to being degassed by three freeze-pump-thaw cycles and dried for 24 h using molecular sieves (3Å) in a glovebox. L-Lactide was purchased from Corbion and was purified by three vacuum sublimations prior to use. Tetrahydrofuran, benzene-d_6 and toluene-d_8 were dried over sodium/benzophenone and distilled under an inert atmosphere prior to being degassed

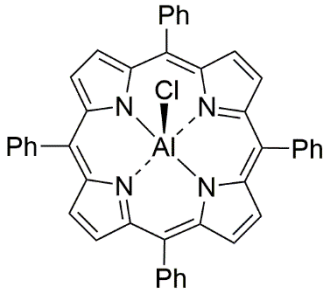
by three freeze-pump-thaw cycles and dried for 24 h using molecular sieves (3Å) in a glovebox.

7.3 Synthesis for Chapter Two

7.3.1 Synthesis of tetraphenylporphyrin aluminum chloride (TPP)AlCl

TPPAlCl was prepared by following the protocol published by Inoue *et al.*[1] 5,10,15,20-Tetraphenylporphyrin (TPP)H_2 was synthesized from freshly distilled pyrrole (4.6 g, 68.0 mmol) and benzaldehyde (7.2 g, 68.0 mmol) in propionic acid (300 mL) under reflux for 4 h. The crude product was precipitated upon standing overnight at room temperature, filtered and then washed with water and methanol (20 mL). The obtained crystals were recrystallized from $CHCl_3$/CH_3OH (1:2 v/v) and dried overnight under vacuum to give TPPH_2 (2.4 g, 23 % yield) as purple crystals.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 8.84 (s, 8H), 8.22 (s, br, 8H), 7.76 (s, 12H), -2.76 (s, 2H).

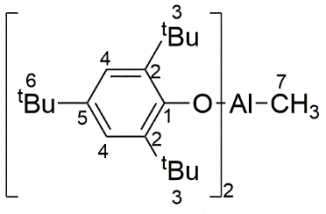


In a glovebox, (TPP)H_2 (1.0 g, 1.6 mmol) was dissolved in CH_2Cl_2 (30 mL) and 1 M diethylaluminium chloride solution in hexane (1.3 g, 1.8 mmol) was added slowly. After 3 h, the volatiles were removed, and the product was washed with hexane and dried overnight to give (TPP)AlCl (1.0 g, 96 % yield) as bright purple crystals.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 9.09 (s, 8H), 8.20 (s, 8H), 7.77 (m, 12H).

In agreement with literature data.[1]

7.3.2 Synthesis of methylaluminum bis(2,4,6-tri-*tert*-butylphenoxy) (MAlBP)



MAlBP was prepared by following the protocol published by Inoue *et al.*[2] 2,4,6-Tri-*tert*-butylphenol was recrystallised from hexane overnight and dried under reduced pressure. 2,4,6-Tri-*tert*-butylphenol (2.0 g, 7.6

mmol) was dissolved in CH_2Cl_2 (15 mL) and 2 M Me_3Al solution in toluene (2.8 mL, 5.5 mmol) was added dropwise by a syringe over 5 min at 0 °C under nitrogen.

The mixture was stirred at room temperature for 3 h, before the volatiles were removed under reduced pressure. A white precipitate was formed, then hexane (10 mL) was added by cannula to the residue and the resulting mixture was stirred at 60 °C, affording a colourless solution, which was then cooled to 0 °C, giving white crystals (1.5 g, 71% yield). The crystals were washed with cold hexane and dried overnight under reduced pressure.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 4H), 1.55 (s, 36H), 1.31 (s, 18H), -0.33 (s, 3H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 152.1 (C^1, 2C), 140.8 (C^2, 4C), 137.6 (C^5, 2C), 122.2 (C^4, 4C), 35.3 (C^3, 4C, C), 32.0 (C^6, 2C, C), 31.9 (C^3, 12C, CH_3), 30.6 (C^6, 6C, CH_3), 29.8 (C^7, 1C).
In agreement with literature data.[2]

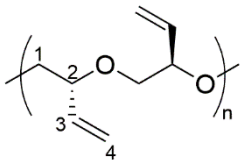
7.3.3 Synthesis of *R or S* isomer of 3,4-epoxy-1-butene


(*R*)-3,4 epoxy-1-butene


(*S*)-3,4 epoxy-1-butene

Enantioenriched 3,4-epoxy-butene were obtained by hydrolytic kinetic resolution using chiral (salen)Co^{III} complex.[3-4] The complex was prepared from commercially available pro-ligands. *(S,S)* or (*R,R*)*N,N'-bis*(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) pro-ligands (1.0 g, 1.6 mmol, 0.015 equiv.) in toluene (8 mL) was treated with acetic acid (1 mL) and stirred under air for 3 h. The crude mixture was left under vacuum overnight. The complex residue obtained was dissolved in racemic 3,4-epoxy-1-butene (7.7 g, 110 mmol). The solution was cooled to 0 °C and H_2O (1.40 mL, 78 mmol, 0.71 equiv.) was added dropwise. After 96 h at room temperature, (*S*) or (*R*)-3,4-epoxy-1-butene (2.50 g, 35.7 mmol, 32%) was isolated by vacuum transfer into a catch flask cooled with liquid N_2. The enantiomeric excess (ee) was determined by chiral HPLC analysis of the 2-naphthylsulfide derivative (obtained by ring-opening of epoxide with 2-napthalenethiol in CH_3OH using 1 equiv. of triethylamine at 0 °C and direct analysis of the product obtained, Chiralcel® OD, 95:5 hexanes:*i*-PrOH, 1 mL/min, 230 nm). The retention time of the *S*- and *R*-enantiomers were 13.2 and 14.5, respectively.

7.3.4 Representative synthesis of poly(epoxybutene) (PEB)



In a glovebox, 3,4-epoxy-1-butene (racemic or enantioenriched) (140 mg 2.0 mmol) was added to (TPP)AlCl (20 μmol, 13.5 mg) in an oven-dried ampoule and the resulting mixture was stirred at ambient temperature for 3 days. The conversion was determined from the crude ^{1}H-NMR spectra using the relative integrations of the -CH-O- peak attributed to the polymer and to the unreacted monomer. CH_2Cl_2 (1 mL) was then added and the mixture was quenched by 1 M HCl/CH_3OH (1:1, 5 mL) and stirred for an additional 1 h. The volatiles were removed under reduced pressure and the residue was dissolved in CH_3OH/CH_2Cl_2 1:1 (1 mL). The resulting solution was filtered to remove insoluble initiator residues. The polymer solution was then purified by gel permeation chromatography using Sephadex LH-20 and CH_3OH/CH_2Cl_2 1:1 as eluent. The volatiles were removed under reduced pressure, and the polymer was dried under vacuum overnight to give a brown oil of atactic PEB or isotactic PEB.

(*i*)-PEB:

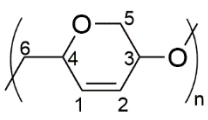
^{1}H-NMR (500 MHz, $CDCl_3$) δ = 5.77-5.69 (m, br, 2H), 5.33-5.13 (m, br, 4H), 4.02-3.91 (m, br, 2H), 3.60-3.38 (m, br, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 136.2 (C^3, 2C), 117.8 (C^4, 2C), 80.8 (C^2, 2C), 72.1 (C^1, 2C).

Diagnostic peaks: 3.60-3.38 (polymer, CH_2O), 2.91 and 2.60 (monomer, CH_2O)

IR (cm^{-1}) = 2280, 2850, 1643, 1452, 1114, 996, 910.

7.3.5 Representative synthesis of functionalisable cyclopolyethers (FCPE)



All reactions were conducted in ampules of volumes at least four times greater than the solution volume. In a 20 mL ampoule, atactic PEB or isotactic PEB (60 mg, 0.9 mmol based on the monomer molecular weight) was stirred for 15 min at 84 °C in 1,2-dichloroethane (DCE) (3.8 mL). Then, second-generation Hoveyda-Grubbs catalyst (27 mg, 43 μmol, 5 mol. %) in DCE (0.5 mL) was added slowly under argon. After 30 min a static vacuum was applied carefully. The reaction progress was monitored by ^{1}H NMR spectroscopy daily. The conversion was determined by ^{1}H-NMR spectroscopy using the relative

integrations of the olefin peaks attributed to the ring-closed polymer and its precursor. After completion, the reaction mixture was cooled to room temperature and 100 equiv. of DMSO (305 μL, 4.3 mmol) was added and the resulting mixture was stirred for 1 h. The volatiles were then removed under reduced pressure, and the residue was dissolved in CH_3OH/CH_2Cl_2 (3:1, 1 mL). The polymer was purified using Sephadex LH-20 and CH_3OH/CH_2Cl_2 3:1 as eluent. The volatiles were removed under reduced pressure, and the polymer was then dried at 60 °C under vacuum overnight to give a brown oil.

(*a*)-FCPE:

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 6.16–5.64 (m, br, 2H), 4.37–3.99 (m, br, 2H), 3.92–3.30 (m, br, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 132.0–124.0 (m, C^1 and C2,), 74.1–73.2 (m, C^3), 71.2–70.4 (m, C^4), 70.4–69.3 (m, C^5), 68–66.6 (m, C^6).

Diagnostic peaks: 6.16–5.64 (CH, RCM polymer), 5.36-5.11 (CH_2, precursor polymer)

(*i*)-FCPE:

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 6.32–5.71 (m, br, 2H), 4.37–3.99 (m, br, 2H), 3.92–3.30 (m, br, 4H).

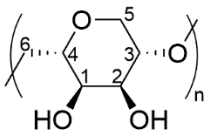
^{13}C-NMR (126 MHz, $CDCl_3$) δ = 131.8 (s, C^1), 125.5 (s, C^2), 73.9 (s, C^3), 70.1 (s, C^5), 69.8 (s, C^4), 67.4 (s, C^6).

Diagnostic peaks: 6.32–5.71 (CH, RCM polymer), 5.33-5.13 (CH_2, precursor polymer)

IR (cm^{-1}) = 2872, 2360, 2162, 2027, 1957, 1718, 1263, 1087, 812, 732.

Modeling of FCPE by ChemBio3D Ultra 14.0 software was done by drawing the 2D structure in Chemdraw Prime 19.0 as drawn in Figure 2.27 then transferring the structure (copy and paste) to the 2D pane of ChemBio3D Ultra 14.0 software to generate the 3D structure automatically.

7.3.6 Representative dihydroxylation of FCPE to PEGose



In a 50-mL round-bottom flask, (*i*)-FCPE (112 mg, 1.0 mmol of the monomer unit) was dissolved in acetone:water (2:1, 6 mL). Then, the desired number of equivalents of dried *N*-methylmorpholine-*N*-oxide was added to the mixture. The reaction mixture was stirred in an ice bath, and then ~100 μL of OsO_4 solution (1% in water) was added slowly and the resultant mixture was stirred for an additional 2 h. The flask was loosely capped, warmed up to the ambient temperature, and stirred overnight. To quench the reaction, sodium sulfide (3 mL of a saturated solution in methanol) was added and continued stirring for 1 h. The mixture was filtered to remove any insoluble residue and the volatiles were evaporated. The polymer solution was purified by GPC using Sephadex G-25 and H_2O as eluent for fully dihydroxylated PEGose and H_2O/CH_3OH 3:1 for 91 and 63% dihydroxylated PEGose. Then, the polymer was dried in a freeze-dryer to give a black coloured solid. The polymer was further purified to reduce the osmium residues level by washing using trioctylamine (TOA) as a scavenger. PEGose (100 mg) was dissolved in 1M HCl (2 mL) and TOA (2 mL) was added. The mixture was shacken vigorously, and the pH was monitored to be acidic using Litmus paper. The organic layer was then extracted with toluene (5 mL). This purification process was repeated twice and then the aqueous phase was neutralized by an aqueous solution of Na_2CO_3 and purified by a Sephadex G-25 column. Then, the polymer was dried in a freeze-dryer to give a pale yellow solid.

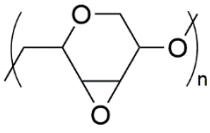
***R,R* or *S,S cis*-PEGose**

^{1}H-NMR (500 MHz, D_2O) δ = 4.43 – 3.61 (m, br, 8H).

^{13}C-NMR (126 MHz, D_2O) δ = 77.9 (s, C^1), 74.7 (s, C^2), 69.2 (s, C^5), 67.2 (s, C^3), 65.1 (s, C^4), 64.0 (s, C^6).

IR (cm^{-1}) = 3344, 2861, 2855, 1140, 1223, 1051.

7.3.7 Epoxidation of FCPE to epoxide cyclopolyether (ECPE)

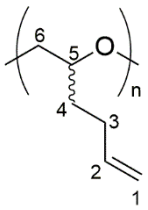


In a 50-mL round-bottom flask, (*i*)-FCPE (448 mg, 4.0 mmol of the monomer unit) was dissolved in dichloromethane (5 mL). Then, *meta*-chloroperoxybenzoic acid (66%, 448 mg, 12.0 mmol) was dissolved in dichloromethane (2 mL) and the resulting solution was added dropwise

to the stirred polymer solution at ambient temperature. After 24 h, the volatiles were removed under reduced pressure, and the residue was dissolved in CH_3OH/CH_2Cl_2 (1:1, 2 mL) and filtered through LH-20 Sephadex column. The volatiles then were removed to give ECPE as a white solid.

^{1}H-NMR (500 MHz, DMSO-d_6) δ = 4.75 – 3.00 (m, br, 8H).
^{13}C-NMR (126 MHz, DMSO-d_6) δ = 83.4 – 59.2 (m, br).

7.3.8 Synthesis of atactic poly(epoxyhexene) (*a*-PEH)

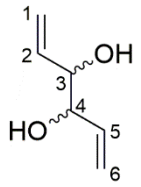


In a glovebox, racemic 1,2-epoxy-5-hexene (200 mg 2.0 mmol) was added to TPPAlCl (20 μmol 13.5 mg) and stirred at the ambient temperature for 72 h. CH_2Cl_2 (1 mL) was then added and the mixture was quenched by 5 mL of 1 M HCl/CH_3OH and stirred for a further 1 h. The volatiles were removed under reduced pressure and the residue dissolved in CH_3OH/CH_2Cl_2 (1:1, 1 mL), before the resulting suspension was filtered to remove insoluble initiator residues. The polymer solution was then purified by gel permeation chromatography using Sephadex LH-20 and CH_3OH/CH_2Cl_2 (1:1) as eluent. The volatiles were removed under low pressure, and the polymer was dried under vacuum. Then, the solid was dissolved in CH_2Cl_2 (1 mL) and precipitated using cold methanol (10 mL) to give a light brown solid of PEH.

^{1} H-NMR (400 MHz, $CDCl_3$) δ = 5.89-5.73 (m, 1H), 5.00 (d, J_{HH}= 17.1, 1H, *trans*), 4.94 (d, J_{HH}= 10.1, 1H, *cis*) 3.76-3.33 (m, 3H), 2.28-2.03 (m, 2H), 1.76-1.48 (m, 2H).
^{13} C-NMR (100 MHz, $CDCl_3$) δ = 138.6 (C^2), 114.7 (C^1), 78.9 (C^6), 72.0 (C^5), 31.5 (C^4), 29.8 (C^3).

7.4 Synthesis for Chapter Three

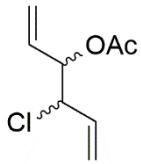
7.4.1 Synthesis of *cis/trans*-1,2-divinylethylene glycol



The compound was prepared following the protocol published by Trost *et al.*[5] Acrolein (30 mL, 448 mmol) was added to a mixture of THF (900 mL) and saturated aqueous ammonium chloride (540 mL). Zinc (58.8 g, 0.90 mol) was added, and the mixture was stirred overnight at room temperature. Then, the mixture was filtered, and the aqueous phase was extracted with CH_2Cl_2 (5 × 250 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The product, a colourless oil (23.3 g, 91%), was purified by vacuum distillation (80 °C and 3 mbar).

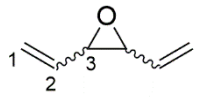
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.88-5.75 (m, 2H), 5.35-5.15 (m, 4H), 4.19 (s, 1H), 3.97 (s 1H), 3.16 (br s, 1H, OH), 2.95 (br s, 1H, OH).
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 136.7 (C^2), 136.0 (C^5), 117.5 (C^1), 117.4 (C^6), 75.9 (C^3), 75.5 (C^4).

7.4.2 Synthesis of 3-chloro-4-acetoxy-1,5-hexadiene



The compound was prepared using the protocol published by Passannante *et al.*[6] Acetyl chloride (15.8 g, 203 mmol) was added to a stirred suspension of calcium chloride (3.5 g, 31 mmol) and 1,5-hexadiene-3,4-diol (19.0 g, 166 mmol) over a period of 45 min. During the addition, the temperature was maintained below 10 °C. The reaction mixture was then stirred for 40 h at room temperature and then 1 h at 50 °C. The dark brown viscous product was poured into ice, neutralized with cold aqueous sodium bicarbonate, extracted with ether, and dried over anhydrous potassium carbonate. After filtration and removal of ether, the crude chloroester was used without further purification.

7.4.3 Synthesis of racemic *cis/trans* divinyl oxirane

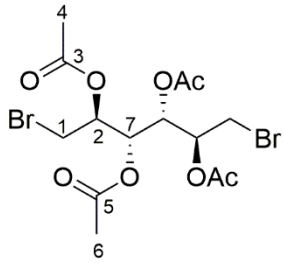


The compound was prepared following Passannante *et al*. protocol.[6] Crude 3-chloro-4-acetoxy-1,5-hexadiene (21.0 g) was suspended in ethylene glycol (60 mL) and slowly added to a two-neck flask, connected to a distillation kit containing sodium hydroxide (28.0 g), potassium hydroxide (28.0 g),

and water (3.0 g). The mixture temperature was maintained at 40-50 °C with a water-bath and the pressure at 13-20 mbar during the addition of the chloroester. The product was collected and trapped in a receiver cooled by liquid nitrogen. Approximately 5 mL of the product-water mixture was collected. Separation of the crude product from water, drying over CaH_2 and distillation under reduced pressure yielded (1.3 g, 35%) of *cis*, *trans*-1,2-divinylethylene oxide and 4,5-dihydrooxepine in a ratio of 20:80, respectively.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.76 - 5.56 (m, 2H), 5.51 (d, J_{HH} =17.2 , 0.20 H, *trans*), 5.48 (d, J_{HH} =17.2 , 0.8 H, *trans*), 5.37 (d, J_{HH} =10.6 , 0.20 H, *cis*), 5.29 (d, J_{HH} =10.3 , 0.80 H, *cis*), 3.53 (d, J_{HH} =6.5 , 0.40 H, *cis*), 3.21 (d, J_{HH} =6.8 , 1.60 H, *trans*)
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 135.1 (C^2, *trans*), 132.4 (C^2, *cis*), 120.9 (C^1, *cis*), 119.5 (C^2, *trans*), 60.4 (C^3, *trans*), 58.9 (C^3, *cis*).

7.4.4 Synthesis of (*2R,3S,4S,5R*)-2,3,4,5-tetraacetoxy-1,6-dibromohexane



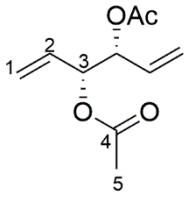
The following procedure was an adaptation of the synthesis carried out by Schmidta *et al.*[7] D-mannitol (54.7 g, 300 mmol) was suspended in dry dioxane (600 mL) under an argon atmosphere. Acetyl bromide (88.9 g, 723 mmol) was added slowly, and the resulting mixture was stirred for 4 days at room temperature. A clear, pale solution was formed. After that, the solution was heated to 40 °C and stirred for another 4 h. Then, the solvent and other volatiles were removed under vacuum. The viscous residue was dissolved in anhydrous pyridine (300 mL), and acetic anhydride (245 g, 2.4 mol) was added slowly. The solution was stirred overnight at room temperature. Then, the mixture was cooled to 0 °C and neutralized by sodium bicarbonate solution (10%) and an aqueous copper sulfate solution (10%, 500 mL) was added. The mixture was extracted by ether (5 * 200 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residuals of pyridine were evaporated under vacuum at 50 °C for 3 h. The orange residue was crystallised from ethanol (50 mL) to afford a white crystalline solid (71.2 g, 50%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 5.36 (d, J_{HH} = 8.1, 2H), 5.05 (m, 2H), 3.49 (dd, J_{HH} = 11.6, 3.8, 2H), 3.30 (dd, J_{HH} = 11.6, 6.0, 2H), 1.98–2.10 (m, 12H).

^{13}C-NMR (125.2 MHz, $CDCl_3$) δ = 168.7 (C^3, 2C), 168.6 (C^5, 2C), 68.2 (C^2, 2C), 68.0 (C^7, 2C), 29.7 (C^1, 2C), 19.8 (C^4, 2C), 19.7 (C^6, 2C).

In agreement with literature data.[7]

7.4.5 Synthesis of (*3R,4R*)-3,4-diacetoxy-1,5-hexadiene



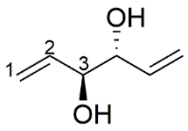
The following procedure was an adaptation of the synthesis carried out by Schmidta *et al.*[7] (*2R,3S,4S,5R*)-2,3,4,5-tetraacetoxy-1,6-dibromohexane (50.2 g, 0.105 mol) was dissolved in glacial acetic acid (525 mL). Sodium acetate (19.0 g, 232 mmol) and zinc dust (27.5 g, 421 mmol) were added. The mixture was heated to 110 °C and stirred until the evolution of gas had ceased and the solution became clear (2 h). After cooling to room temperature, the zinc dust was filtered off and the acetic acid was removed under vacuum. The viscous, colourless residue was dissolved in water and extracted with diethyl ether (3 x 150 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The colourless crude product was distilled under vacuum (90 °C, 20 mbar) to afford the product as a colourless liquid (17.7 g, 81%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 5.70 (ddd, J_{HH} = 17.2, 10.7, 6.0, 2H), 5.36 (d, J_{HH} = 5.1, 2H), 5.30 (d, J_{HH} = 17.2, 2H), 5.24 (d, J_{HH} = 10.7, 2H), 2.09 (s, 6H).

^{13}C-NMR (125.2 MHz, $CDCl_3$) δ = 169.6 (C^4, 2C), 131.9 (C^2, 2C), 119.0 (C^1, 2C), 74.3 (C^3, 2C), 20.9 (C^5, 2C).

In agreement with literature data.[7]

7.4.6 Synthesis of (*3R,4R*)-3,4-dihydroxy-1,5-hexadiene

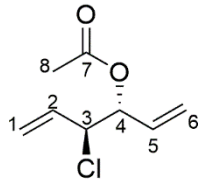


The following procedure was an adaptation of the synthesis carried out by Schmidta *et al.*[7] (*3R,4R*)-3,4-Diacetoxy-1,5-hexadiene (13.0 g, 65.0 mmol) was dissolved in methanol (260 mL), and an aqueous solution of potassium hydroxide (2 M, 4 mL) was added. The progress was monitored by TLC (eluent: *n*-hexane/ethyl acetate, 1:1). After starting material consumption (approx. 3 h), aqueous HCl (1 M, 8 mL) was added in 1 mL portions. The mixture was

dried over $MgSO_4$, filtered and the solvent was carefully removed under reduced pressure until the solution became turbid. Diethyl ether was added, and the solution was dried over $MgSO_4$ again and filtered. The solvent was removed under vacuum and a pale crude product is distilled under vacuum (80 °C, 3 mbar) to afford the product as a colourless oil (6.4 g, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.83 (m, 2H), 5.33 (d, J_{HH} = 17.2, 2H), 5.22 (d, J_{HH} = 10.6, 2H), 3.96 (m, 2H), 3.40 (br, s, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 136.7 (C^2, 2C), 117.4 (C^1, 2C), 75.9 (C^3, 2C).
In agreement with literature data.[7]

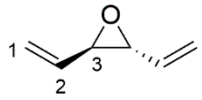
7.4.7 Synthesis of (*3S,4R*)-3-chloro-4-acetoxy-1,5-hexadiene



Acetyl chloride (4.9 g, 63 mmol) was added to a stirred suspension of calcium chloride (896 mg, 8 mmol) and (*3R,4R*)-3,4-dihydroxy-1,5-hexadiene (6.0 g, 52 mmol) over a period of 45 min. During the addition, the temperature was maintained below 10 °C using a cooling circulating bath. The reaction mixture was then stirred for 40 h at room temperature and then 1 h at 50 °C. The dark brown viscous product was poured into ice, neutralized with cold, aqueous sodium bicarbonate. The resulting mixture was extracted with ether and dried over anhydrous potassium carbonate. After filtration and removal of ether by vacuum, the crude chloroester was purified using silica column to afford (2.8 g, 30 %) yield as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.87-5.73 (m, 2H), 5.41-5.24 (m, 4H), 5.21 (dd, J_{HH} =8.1, 5.4 1H), 4.36-4.33 (dd, J_{HH} =8.1, 5.4, 1H), 2.05 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 169.6 (C^7), 133.9 (C^2), 131.9 (C^5), 120.1 (C^1), 120.4 (C^6), 76.0 (C^3), 62.9 (C^4), 20.9 (C^8).

7.4.8 Synthesis of enantiopure *trans* (*3R,4R*)-divinyl oxirane



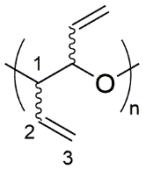
(*3S,4R*)3-chloro-4-acetoxy-1,5-hexadiene (2.1 g) was suspended in ethylene glycol (20 mL) and slowly added to a two-necked flask, connected to a distillation kit containing sodium hydroxide (8.0 g), potassium hydroxide (8.0 g), and water (1.0 g). The mixture temperature was maintained at 40-

50 °C by a water-bath and the pressure at 13-20 mbar during the addition of the chloroester. The product was collected and trapped in a receiver cooled by liquid nitrogen. Approximately 0.6 mL of product-water-solvents mixture was collected containing traces of dioxane.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.61 (m, 1H), 5.48 (d, J_{HH} = 16.4, 1H), 5.29 (d, J_{HH} = 11.0, 1H), 3.25 (d, J_{HH} = 6.8, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 135.1 (C^2, 2C), 119.5 (C^1, 2C), 60.4 (C^3, 2C).

7.4.9 Ring-opening polymerisation of racemic divinyl oxirane



In a glovebox, racemic 1,2-divinyl oxirane (96 mg 1.0 mmol) was added to TPPAlCl (0.01 mmol, 6.8 mg) in an oven-dried ampoule and stirred at the ambient temperature for 2 h. Then, MAlBP (5.6 mg, 0.01 mmol) was added. Outside the glovebox, the mixture was heated at 60 °C for 10 d. Then, it was cooled to ambient temperature. After that, CH_2Cl_2 (1 mL) was then added and the mixture quenched by 5 mL of 1 M HCl/CH_3OH and stirred for a further 1 h. The volatiles were removed under reduced pressure and the residue dissolved in CH_3OH/CH_2Cl_2 (1:1, 1 mL), and the resulting suspension was filtered to remove insoluble initiator residues. The polymer solution was then purified by gel permeation chromatography using Sephadex LH-20 and CH_3OH/CH_2Cl_2 (1:1) as the eluent. The volatiles were removed, and the polymer was dried under vacuum to give a brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.00-5.70 (m, br, 2H), 5.37-5.00 (m, br, 4H), 3.98 (m, br, 2H).

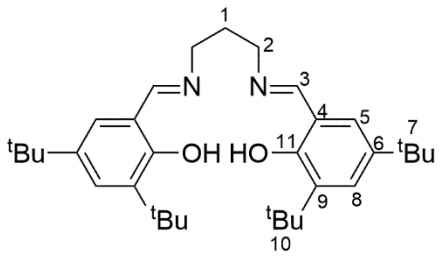
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 137.6 (C^2, br, 2C), 117.4 (C^3, br, 2C), 80.7 (C^1, br, 2C).

7.5 Synthesis for Chapter Four

7.5.1 General method for the synthesis of aluminium-salen catalysts

In a glovebox, one equiv. of trimethyl aluminium 2M solution in toluene was added dropwise to a vigorously stirring solution of the respective pro-ligand in toluene, in a Schlenk flask. After bubbling had subsided, the Schlenk flask was sealed and removed from the glovebox. The reaction vessel was immersed in a preheated oil bath at 110 °C. After heating and stirring for 16 h, the reaction was allowed to cool to room temperature. Once the product was observed to crystallise from solution, the remainder of the solution was removed by cannula filtration and the product washed with hexane three times before being dried under vacuum. If no product was observed, *ca.* three quarters the solvent was removed before being replaced with hexane and being cooled to 0 °C. The product was then isolated in the same fashion as described above.

7.5.2 Synthesis of *N,N'-bis*(3,5-di-*tert*-butylsalicylidene)-1,3-propanediamine[8]



1,3-Diaminopropane (0.73 g, 9.8 mmol) was added rapidly to a stirring solution of 3,5-di-*tert*-butylsalicylaldehyde (4.6 g, 19.6 mmol) in ethanol (50 mL). After refluxing for 4 h at 78 °C the precipitated solid was filtered, washed with cold ethanol and dried under vacuum to yield the desired product (4.6 g, 85 %).

Pro-ligand:

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 13.82 (s, 2H), 8.40 (d, J_{HH} = 1.3, 2H), 7.40 (d, J_{HH} = 2.5, 2H), 7.10 (d, J_{HH} = 2.5, 2H), 3.72 (td, J_{HH} = 6.6, 1.2, 4H), 2.14 (q, J_{HH} = 6.6, 2H), 1.47 (s, 18H), 1.32 (s, 18H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 166.6 (C^{11}, 2C), 158.3 (C^{4}, 2C), 140.2 (C^{9}, 2C), 136.8 (C^{6}, 2C), 127.0 (C^{5}, 2C), 126.0 (C^{8}, 2C), 118.0 (C^{3}, 2C), 56.9 (C^{2}, 2C), 35.2 (C^{1}, 1C), 34.3 (C^{10}, 2C), 31.9 (C^{7}, 2C), 31.7 (C^{10}, 6C, CH_3), 29.6 (C^{7}, 6C, CH_3).

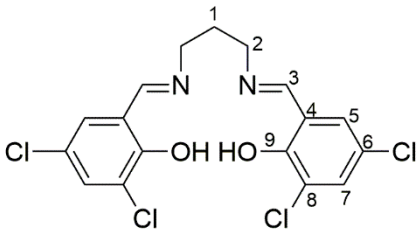
Catalyst:

^{1}H-NMR (500 MHz, C_6D_6) δ = 8.75 (s, 2H), 7.75 (d, J_{HH} = 2.7, 1H), 7.34 (s, 1H), 6.89 (d, J_{HH} = 2.7, 2H), 3.07-2.79 (m, 2H), 2.75-2.38 (m, 2H), 1.86 (s, 18H), 1.57-1.43 (m, 2H) 1.39 (s, 18H), -0.53 (s, 3H).

^{13}C-NMR (126 MHz, C_6D_6) δ = 170.1 (2C), 164.1 (2C), 141.3 (2C), 137.5 (2C), 130.2 (2C), 127.4 (2C), 118.9 (2C), 54.9 (2C), 35.9 (1C), 34.1 (2C), 31.7 (2C), 30.2 (6C), 27.4 (6C), -9.2 (1C).

In agreement with literature data.[8]

7.5.3 Synthesis of *N,N'-bis*(3,5-di-chlorosalicylidene)-1,3-propanediamine[8]



Synthesised using 1,3-diaminopropane (0.73 g, 10 mmol) and 3,5-dichlorosalicylaldehyde (3.82 g, 20 mmol) in ethanol (50 mL). After refluxing for 4 h at 78 °C the precipitated solid was filtered, washed with cold ethanol and dried under vacuum to yield the desired product (3.85 g, 93 %).

Pro-ligand:

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 14.32 (s, 2H), 8.31 (s, 2H), 7.44-7.39 (m, 2H), 7.18-7.14 (m, 2H), 3.78 (m, 4H), 2.20-2.10 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 164.3 (C^9, 2C), 156.8 (C^8, 2C), 132.5 (C^6, 2C), 129.1 (C^4, 2C), 123.0 (C^5, 2C), 122.9 (C^7, 2C), 119.5 (C^3, 2C), 56.1 (C^2, 2C), 31.4 (C^1, 1C).

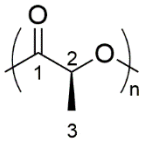
Catalyst:

^{1}H-NMR (500 MHz, CD_2Cl_2) δ = 8.12 (s, 2H), 7.45 (d, J_{HH} = 2.6, 2H), 7.11 (d, J_{HH} = 2.6, 2H), 4.24-4.17 (m, 2H), 3.67-3.72 (m, 2H), 2.24-1.99 (m, 2H), -0.66 (s, 3H).

^{13}C-NMR (126 MHz, CD_2Cl_2) δ = 167.6 (2C), 159.8 (2C), 141.4 (2C), 134.6 (2C), 130.4 (2C), 127.1(2C), 120.3 (2C), 60.6 (2C), 30.6 (1C), -9.5 (1C).

In agreement with literature data.[8]

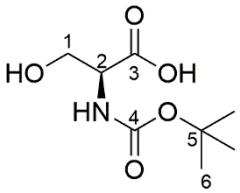
7.5.4 Ring-opening polymerisation of L-LA to PLLA



In a glovebox L-lactide (434 mg, 3.0 mmol), catalyst **4.30** (13.8 mg, 0.030 mmol) and benzyl alcohol (3 mg, 30 μmol) were dissolved in toluene (1.5 mL) and added to an oven-dried ampoule. Outside the glovebox, the mixture was heated at 85 °C for 2 h. Then, it was cooled to the ambient temperature and quenched by the addition of a few drops of methanol and the product was precipitated in a large amount of cold methanol (*ca*. 100 mL) to yield PLLA as a white solid. The polymer was filtered and dried under reduced pressure (390 mg – 90%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 5.16 (q, J_{HH} = 7.1, 1H), 1.58 (d, J_{HH} = 7.1, 3H).
^{13}C-NMR (126 MHz, $CDCl_3$) δ = 169.6 (C^1), 69.0 (C^2), 16.6 (C^3).
In agreement with literature data.

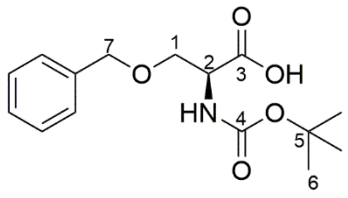
7.5.5 Synthesis of *N*-Boc-L-serine



The following procedure was an adaptation of the synthesis carried out by Yamada *et al*.[9] A solution of L-serine (15.6 g, 148 mmol) in 1 M aqueous NaOH (150 mL), and di-*tert*-butyl dicarbonate (39.3 g, 180 mmol) in 1,4-dioxane (300 mL) was prepared. The stirred solution of L-serine was cooled to 0 °C, and the di-*tert*-butyl di-carbonate solution was added dropwise through a dropping funnel. The mixture was warmed up to room temperature and stirred overnight. The organic layer was separated, and the aqueous layer was washed with Et_2O (150 mL), acidified with 1 M H_2SO_4 to pH 3 and extracted with ethyl acetate (4 * 200 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to generate a colourless gel of *N-(tert*-butoxycarbonyl)-L-serine (29.4 g, 96 % yield).

^{1}H-NMR (400 MHz; $CDCl_3$) δ = 6.54 (br s, 1H), 5.53 (br s, 1H), 4.34-4.04 (m, 1H), 3.88 (m, 2H), 1.47 (s, 9H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 173.9 (C^4), 156.3 (C^3), 80.7 (C^2), 62.0 (C^1), 55.5 (C^5), 28.3 (C^6, 3C).
In agreement with literature data.[9]

7.5.6 Synthesis of *N*-Boc-*O*-benzyl-L-serine



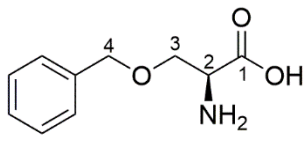
The following procedure was an adaptation of the synthesis carried out by Wang *et al*.[10] A solution of *N*-Boc-L-serine (29.4 g, 143 mmol) in anhydrous DMF (250 mL) was prepared and cooled to 0 °C. Anhydrous sodium hydride (60%, 13.0 g, 330 mmol) was dissolved in anhydrous DMF (250 mL) and was added to the *N*-Boc-L-serine solution under argon atmosphere at 0 °C. The mixture was stirred until the evolution of hydrogen gas had ceased. Benzyl bromide (18.7 mL, 157 mmol) was added dropwise *via* syringe at 0 °C. The reaction was allowed to reach room temperature and was stirred for 18 h. The resultant clear solution was poured into iced water (1 L). This mixture was extracted with diethyl ether (4 * 250 mL). The aqueous phase was acidified to pH 3 with citric acid (50.0 g), saturated with NaCl and extracted with ethyl acetate (6 * 250 mL). The combined organic layers were washed with 0.01 M NH_4OAc (solution pH: 7.2 * 100 mL) and water (2 * 150 mL), dried ($MgSO_4$) and evaporated under reduced pressure to a total volume of ca. 100 mL. Hexane (400 mL) was added to give the crystalline product of yield *N*-Boc-*O*-Benzyl-L-serine which was filtered and dried (31.1 g, 73 % yield).

^{1}H-NMR (400 MHz; $CDCl_3$) δ = 7.51-7.16 (m, 5H), 5.39 (t, J_{HH} = 7.6, 1H), 4.56 (s, 2H), 3.92 (br, s, 1H), 3.72-3.70 (m, 2H), 1.45 (s, 9H).

^{13}C-NMR (100 MHz; $CDCl_3$) δ = 175.5 (C^4), 155.7 (C^3), 137.3 (Ar, 1C), 128.4 (Ar, 2C), 127.8 (Ar, 2C), 127.6 (Ar, 1C), 80.3 (C^2), 73.4 (C^1), 69.7 (C^7), 53.8 (C^5), 28.3 (C^6, 3C).

In agreement with literature data.[10]

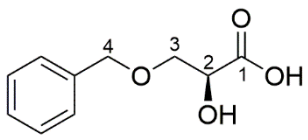
7.5.7 Synthesis of *O*-benzyl-L-serine



The following procedure was an adaptation of the synthesis carried out by Yamada *et al*.[9] *N*-Boc-*O*-Benzyl-L-serine (31.0 g, 105 mmol) was dissolved in CH_2Cl_2 (125 mL). Trifluoroacetic acid (15.3 mL, 200 mmol) was added and the reaction was stirred overnight at room temperature. The solvent was removed under reduced pressure to yield *O*-benzyl-L-serine as a clear yellow oil (16.4 g, 80 %), and used without further purification.

^{1}H-NMR (400 MHz; D_2O) δ = 7.36-7.57 (m, 5H), 4.65 (s, 2H), 4.03-3.94 (m, 3H).
^{13}C-NMR (100 MHz; D_2O) δ = 170.8 (C^1), 128.9 (Ar, 1C), 128.5 (Ar, 2C), 127.9 (Ar, 2C), 127.6 (Ar, 1C), 72.7 (C^2), 68.2 (C^3), 53.9 (C^4).
In agreement with literature data.[9]

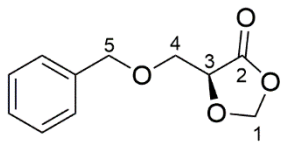
7.5.8 Synthesis of 2-hydroxy-3-(phenyl-methoxy) propanoic acid



The following procedure was an adaptation of the synthesis carried out by Matthes *et al.*[11] *O*-benzyl-L-serine (16.0 g, 82.0 mmol) was dissolved in 0.5 M aqueous H_2SO_4 solution (350 mL) and the resulting solution cooled to 0 °C. A solution of sodium nitrite (34.0 g, 0.5 mol) in water (120 mL) was added dropwise to the previous solution with stirring. The reaction was stirred at 0 °C for 3 h, before being allowed to reach room temperature. The reaction was stirred overnight and then extracted with Et_2O (5 * 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield 2-hydroxy-3-(phenyl-methoxy) propanoic acid as a yellow oil (12.0 g, 74 %).

^{1}H-NMR (500 MHz; DMSO-d_6) δ = 7.28-7.4 (m, 5H), 4.61 (d, J_{HH} = 8.1, 2H), 4.21 (dd, J_{HH} = 2.7, 2.2, 1H), 3.83 (dd, J_{HH} = 6.6, 2.7, 1H), 3.78 (dd, J_{HH} = 6.6, 2.2, 1H).
^{13}C-NMR (100 MHz; Acetone-D_6) δ = 173.4 (C^1), 138.8 (Ar, 1C), 128.4 (Ar, 2C), 127.6 (Ar, 2C), 127.7 (Ar, 1C), 73.1 (C^2), 72.3 (C^3), 70.8 (C^4).
In agreement with literature data.[11]

7.5.9 Synthesis of benzyloxymethyl-DOX

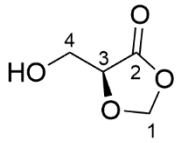


The following procedure was an adaptation of the synthesis carried out by Cairns *et al.*[12] Paraformaldehyde (3.20 g, 107 mmol), *para*-toluene sulforic acid monohydrate (1.21 g, 7 mmol) were dissolved in benzene (250 mL) and refluxed at 95 °C in a Dean-Stark apparatus. 2-Hydroxy-3-(phenylmethoxy) propanoic acid (14.0 g, 71.3 mmol) was dissolved in benzene (50 mL) and the resulting solution added dropwise to the previous refluxed mixture. The reaction conversion monitored by TLC which showed a completion after 3 h. The mixture was allowed to cool to room temperature and

washed with 10 % aqueous sodium bicarbonate solution (2 * 100 mL), water (2 * 100 mL) and brine (2 * 100 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to yield the crude benzyloxymethyl-DOX (11.4 g, 75 % yield).

^{1}H-NMR (400 MHz; $CDCl_3$) δ = 7.29-7.39 (m, 5H), 5.60 (s, 1H), 5.48 (s, 1H), 4.59 (s, 2H), 4.38 (t, J_{HH} = 4.0, 1H), 3.80-3.90 (m, 2H).
^{13}C-NMR (100 MHz; $CDCl_3$) δ = 171.1 (C^2), 137.3 (Ar, 1C), 128.3 (Ar, 1C), 127.7 (Ar, 1C), 127.4 (Ar, 1C), 95.6 (C^1), 73.5 (C^3), 73.3 (C^4), 68.9 (C^5).

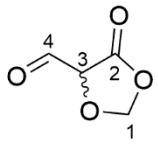
7.5.10 Synthesis of hydroxymethyl-DOX



Benzyloxymethyl-DOX (11.0 g, 53.0 mmol) was dissolved in EtOAc (50 mL), Pd/C 10 % (250 mg) and acetic acid (1 g) were added. The reaction was stirred at room temperature under hydrogen atmosphere (1 atm) for 24 h. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to yield the product which was used without further purification (4.7 g, 76 % yield).

^{1}H-NMR (400 MHz; $CDCl_3$) δ = 5.58 (s, 1H), 5.45 (s, 1H), 4.29 (t, J_{HH} = 4.3, 1H), 3.94 (d, 3.9, 2H).
^{13}C-NMR (100 MHz; $CDCl_3$) δ = 171.7 (C^2), 95.5 (C^1), 74.5 (C^3), 61.3 (C^4).

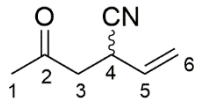
7.5.11 Synthesis of aldehyde-DOX



Hydroxymethyl-DOX (1.2 g, 10.0 mmol) was dissolved in CH_2Cl_2 (10 mL). Then, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) (310 mg, 2 mmol) and *bis*(acetoxy)iodobenzene (BAIB) (350 mg, 12 mmol) were added and the mixture was stirred for 48 h at room temperature. Then it was diluted with CH_2Cl_2 (5 mL). The mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The mixture was purified by column chromatography using petroleum ether/ethyl acetate (9:1) to give the desired aldehyde (350 mg, 30 % yield).

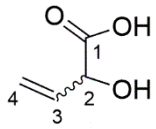
^{1}H-NMR (500 MHz; $CDCl_3$) δ = 9.87 (s, 1H), 5.66 (s, 1H), 5.55 (s, 1H), 5.30 (s, 1H).
^{13}C-NMR (126 MHz; $CDCl_3$) δ = 188.5 (C^4), 164.4 (C^2), 93.1 (C^1), 79.6 (C^3).

7.5.12 Synthesis of 2-acetoxy-3-butenenitrile



The following procedure was an adaptation of the synthesis carried out by Stach *et al.*[13] Acetic anhydride (14.3 mL, 150 mmol) was added dropwise (7-8 min) with vigorous stirring to acrolein (10 mL, 100 mmol) in toluene (30 mL) at -10 °C using a cooling circulating bath. NaCN (11.0 g, 225 mmol) in H_2O (60 mL) was then added dropwise while keeping the temperature at -10 °C to the resulting mixture. After stirring for 3 h the phases were separated, and the aqueous phase was extracted with toluene (3 * 10 mL). The combined organic layers were washed with 1 M aqueous acetic acid (2 * 10 mL), saturated aqueous Na_2CO_3 solution (2 * 10 mL), and H_2O (2 * 10 mL). After drying over $MgSO_4$, the solvent was removed yielding 2-acetoxy-1-cyanobut-3-ene (14.8 g, 80%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.90-5.72 (m, 3H), 5.55 (m, 1H), 2.16 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 169.0 (C^2), 128.1 (C^5), 122.2 (C^6), 115.2 (C^4), 61.6 (C^3), 20.5 (C^1).
In agreement with literature data.[13]

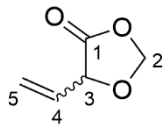
7.5.13 Synthesis of vinyl glycolic acid



The following procedure was an adaptation of the synthesis carried out by Li *et al.*[14] To a stirred solution of 2-acetoxy-3-butenenitrile (20.0 g, 160 mmol) concentrated aqueous HCl (20 mL) was added dropwise over 30 min at room temperature. After the addition was complete, the solution was stirred overnight at 70-75 °C. The resulting dark brown mixture was allowed to cool to room temperature, and water was added (5 mL). The solution was then extracted 10 times with 30 mL portions of ether, and the ethereal layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (16.1 g, 95 %) of crude acid as a pale yellow liquid which was used in the next step without purification.
^{1}H-NMR (400 MHz, D_2O) δ = 5.92 (m, 1H), 5.37 (d, J_{HH} = 17.0, 1H), 5.26 (d, J_{HH} = 9.8, 1H), 4.69 (d, J_{HH}= 4.1, 1H).
^{13}C-NMR (100 MHz, D_2O) δ = 176.1 (C^1), 134.3 (C^3), 119.0 (C^4), 72.7 (C^2).

In agreement with literature data.[13]

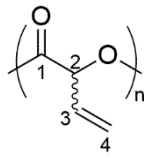
7.5.14 Synthesis of vinyl-DOX from vinyl glycolic acid



Paraformaldehyde (9.4 g, 310 mmol), *para*-toluene sulforic acid monohydrate (3.0 g, 15.7 mmol) was dissolved in DCE (250 mL) and refluxed in a reverse Dean-Stark apparatus. Vinylglycolic acid (16.0 g, 157 mmol) was dissolved in DCE (50 mL) and added dropwise to the refluxing mixture over 50 min. The reaction conversion was monitored by TLC, which showed completion after 3 h. The mixture was allowed to cool to room temperature and washed by a 10% aqueous sodium bicarbonate solution (2 * 100 mL), water (2 * 100 mL) and brine (2 * 100 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to yield the crude vinyl-DOX (12.5 g, 70 % yield). The product was dried over calcium hydride overnight and purified by vacuum distillation (2 mbar at 45 °C).

^{1}H-NMR (400 MHz; $CDCl_3$) δ = 5.89-5.80 (m, 1H), 5.54 (d, J_{HH} = 17.8, 1H), 5.53 (s, 1H), 5.48 (s, 1H), 5.41 (d, J_{HH} = 9.8, 1H) 4.68 (d, J_{HH} = 5.2, 1H).
^{13}C NMR (100 MHz; $CDCl_3$) δ = 170.9 (C^1), 129.1 (C^4), 120.1 (C^5), 94.5 (C^2), 73.7 (C^3).
IR (cm^{-1}) = 2980, 2940, 2890, 1755, 1655, 1475, 1435, 1375, 1350, 1340, 1310, 1270, 1235, 1160, 1120, 1010, 990, 940, 830.
HRMS (ESI) for $C_5H_6O_3$:114.0993, found: 114.0990.

7.5.15 Representative ROP of vinyl-DOX to poly(vinylglycolic) acid

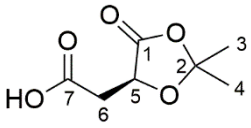


In a glovebox vinyl-DOX (570 mg, 5 mmol), catalyst **4.30** (46 mg, 0.1 mmol) and benzyl alcohol (10 mg, 0.1 mmol) were added to an oven-dried ampule. Outside the glovebox, a static vacuum was applied, then the mixture was heated at 90 °C for 72 h. Then, it was cooled to the ambient temperature and quenched with the addition of a few drops of methanol and then purified by Sephadex LH-20 using CH_3OH/CH_2Cl_2 (1:1) as eluent. The solvent was evaporated under reduced pressure to give the polymer as pale oil.

^{1}H-NMR (400 MHz, $CDCl_3$); δ = 6.20-5.70 (br, s, 1H), 5.77-5.65 (br, s, 1H), 5.64-5.25 (br, m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$); δ = 166.8 (C^1), 128.6 (C^3), 121.2(C^4), 73.7 (C^2).

7.5.16 Synthesis of enantiopure carboxy methyl-DOX



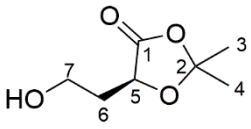
The following procedure was an adaptation of the synthesis carried out by Denmark *et al.*[15] L-Malic acid (5.0 g, 37.3 mmol), paraformaldehyde (1.7 g, 56.0 mmol), and *para*-toluene sulforic acid monohydrate (70 mg, 370 μmol) were dissolved in benzene (150 mL) and refluxed at 95 °C in a Dean-Stark apparatus. The reaction conversion was monitored by TLC which showed completion after 2 h. The mixture was allowed to cool to room temperature and washed with 10 % aqueous sodium bicarbonate solution (50 mL). The aqueous phase was extracted by CH_2Cl_2 (3 * 50 mL) and the combined organic was concentrated under reduced pressure. The crude residue was purified by silica column using ethyl acetate: petroleum.ether/acetic acid (69:30:1) as eluent. The purified product was dissolved in 25 mL of CH_2Cl_2 and stirred strongly while 150 mL of hexane was being added slowly to afford the product as a white solid which was filtered and dried to give the desired product (4.3 g, 78% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.70 (dd, J_{HH} = 5.6, 3.3, 1H), 3.01 (dd, J_{HH} = 14.0, 3.2, 1H), 2.85 (dd, J_{HH} = 14.0, 5.6, 1H), 1.61, (s, 3H), 1.57 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 174.6 (C^7), 171.7 (C^1), 111.3 (C^2), 70.3 (C^5), 35.8 (C^6), 26.8 (C^3), 25.9 (C^4).

In agreement with literature data.[15]

7.5.17 Synthesis of enantiopure hydroxy ethyl-DOX

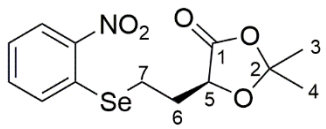


The following procedure was an adaptation of the synthesis carried out by Denmark *et al.*[15] In a three-necked, 150-mL round-bottom flask fitted with an N_2 inlet adapter, a thermocouple (inserted through a septum), a pressure-equalizing addition funnel with rubber septum and a magnetic stir bar was placed a solution of enantiopure carboxy methyl-DOX (4.0 g, 27.4 mmol) in THF (25 mL) at 0 °C (ice bath). A solution of

borane in THF (1.0 M in THF, 27.5 mL, 27.5 mmol, 1.1 equiv.) was then added dropwise over 1.5 h through the addition funnel as gentle bubbling was observed. After complete addition of the borane solution, the mixture was stirred at 0 °C for 2.5 h and was then warmed to room temperature. After being stirred for 8 h the reaction was quenched by the dropwise addition of methanol (20 mL). The reaction mixture was concentrated to give a crude oil, which was purified by chromatography on silica gel (EtOAc/hexane, 1:1 to 7:3) to afford the product as a colourless oil (1.5 g, 42%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.54 (t, J_{HH}= 3.8, 1H), 3.80, (m, 2H), 2.04 (m, 2H), 1.59 (s, 3H), 1.52 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 173.8 (C^1), 115.1 (C^2), 72.0 (C^5), 58.6 (C^7), 34.1 (C^6), 26.0 (C^3), 25.2 (C^4).
In agreement with literature data.[15]

7.5.18 Synthesis of enantiopure o-nitrophenyl selenide ethyl-DOX[16]

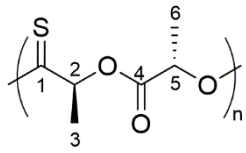


A solution of hydroxy ethyl-DOX (0.5 g, 3.7 μmol) in 2.0 mL of tetrahydrofuran containing *o*-nitrophenyl selenocyanate (1.0 g, 4.5 mmol) under nitrogen was treated dropwise with *tri*-n-butylphosphine (0.9 g, 4.5 mmol) at room temperature. After the reaction was stirred for 2 h, the solvent was removed *in vacuo*. Chromatography of the residue on silica gel using ether/ petroleum ether (1:1) gave *o*-nitrophenyl selenide ethyl-DOX (0.6 g, 47%) as an orange crystalline compound.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.3 (d, J_{HH} = 8.1, 1H), 7.55 (s, 2H), 7.34 (m, 1H), 4.56 (t, J_{HH} = 11.8, 1H), 3.04 (t, J_{HH} = 16.6, 2H), 2.26 (m, 2H), 1.66 (s, 3H), 1.57 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 172.5 (C^1), 134.0 (Ar, 1C), 132.5 (Ar, 1C), 128.8 (Ar, 1C), 126.7 (Ar, 1C), 125.8 (Ar, 2C), 111.1 (C^2), 73.7 (C^5), 30.8 (C^7), 27.3 (C^6), 25.8 (C^3), 20.4 (C^4).

7.6 Synthesis for Chapter Five

7.6.1 Ring-opening polymerisation of thionolactide



In a glovebox, L-thionolactide (320 mg, 2.0 mmol), catalyst **4.30** (36.8 mg, 80 μmol) and benzyl alcohol (2 μL, 20 μmol) were dissolved in 2 mL of toluene and added to an oven-dried ampoule. Outside the glovebox, the mixture was heated at 55 °C for 7 h. Then, it was cooled to ambient temperature and quenched with the addition of a few drops of methanol and then precipitated out by cold methanol (25 mL, -70 °C) to give a white solid (290 mg – 90%) of poly(thionolactide).

^{1}H-NMR (500 MHz, C_6D_6); δ = 5.68 (q, J_{HH} = 7.0, 1H), 5.35 (q, J_{HH} = 6.8, 1H), 1.47 (d, J_{HH} = 7.0, 3H), 1.43 (d, J_{HH} = 6.8, 3H).

^{13}C-NMR (126 MHz, C_6D_6); δ = 218.4 (C^1), 168.2 (C^4), 76.8 (C^2), 75.3 (C^5), 19.8 (C^3), 16.6 (C^6).

7.7 References

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